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14. ABSTRACT

The *American Institute for Medical and Biological Engineering-Military Collaboration: Bioengineering Challenges of Brain Trauma* was held February 20, 2008, at the National Academy of Sciences in Washington, D.C. The one-day meeting featured speakers and panelists discussing state of the art technology for addressing imaging, monitoring and rehabilitation therapy for traumatic brain injury as it relates to medical and biological engineering. The meeting also featured discussions of the policy implications involved with new technologies and the potential benefit to the general public. The meeting was a successful forum to connect AIMBE's Fellows and USAMRMC TATRC's experts, as well as other attendees, including members of the media, and will lead to a collaborative working group for information exchange between both parties.

15. SUBJECT TERMS
Meeting, Brain Trauma, Collaboration

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Introduction

On February 20, 2008, the American Institute for Medical and Biological Engineering (AIMBE) held a meeting in conjunction with the US Army Medical Research and Materiel Command's Telemedicine and Advanced Technology Research Center (TATRC) titled *AIMBE-Military Collaboration: Bioengineering Challenges of Brain Trauma* at the National Academy of Sciences in Washington D.C. The meeting was a satellite meeting to the AIMBE 2008 Annual Event, *The Global Impact of Medical and Biological Engineering*.

Working together, AIMBE and TATRC held a successful meeting where knowledge was shared to accelerate the development of new diagnostic and therapeutic treatments for the brain-injured patient. This will ultimately benefit the health and well being of members of the public who may suffer from traumatic brain injury, as well as increase public knowledge about new technological developments and their application to improving health.

One of the primary goals of the meeting was to introduce AIMBE's leading minds to military researchers for possible future collaboration on state of the art research benefiting soldiers and the public. The meeting drew an attendance of approximately 100 individuals, primarily from the United States and from a wide range of backgrounds, including medical and biological engineers, students, military personnel and members of the media.

The military has pioneered the management of trauma patients. The goal of this conference was to identify state-of-the-art methods in monitoring, imaging, and rehabilitation technology, applicable to the brain trauma patient, and to connect civilian innovators with military experts to share cutting edge technological advances.

AIMBE represents multiple engineering and scientific societies and its Fellows provide a broad range of engineering, scientific and medical expertise to the public. Through this network, AIMBE represents approximately 50,000 individuals engaged in medical and biological engineering. AIMBE's goal is to increase public understanding of the principles and practice of medical and biological engineering.

Body

The accomplishments associated with this meeting included the presentation of new research in several key areas, as well as moderated discussion on the implications and implementation of these technologies. Presentations and panel discussions are included in the transcript, included as Appendix B.

The topics covered included the current state of each technology and their respective challenges and policy implications. Following is a list of the presentations made to attendees (Appendix A). Speakers did not provide abstracts, though they were requested to do so. The list below includes the title of each presentation, full copies of which are available as part of the addendum. Bios are included as part of the program document distributed to attendees (Appendix C). All of the biographies and presentations are available at www.aimbe.org/tatrcmeeting.

The conference helped to establish relationships between military healthcare providers, the engineering community, and civilian experts in the care of brain-injured patients, as opposed to presenting research findings as traditional meetings are focused. The conference also focused on information exchange and discussion.

General Overview

The US Military has pioneered the treatment of traumatic brain injury. Recent advances in physiologic monitoring, imaging, and rehabilitation therapeutics are currently being explored in both civilian and military healthcare systems for their application to the diagnosis and treatment of traumatic brain injury. During this meeting, AIMBE and TATRC exchanged information which may be relevant to military physicians who are active in the diagnosis and treatment of traumatic brain injury, and civilian neurosurgeons, neurologists, rehabilitation specialists, radiologists, imaging experts, and bioengineers that are developing state-of-the-art techniques to improve the diagnosis and treatment of brain trauma patients.

This conference brought together leaders in military neurotrauma research and treatment to identify promising technologies which might be rapidly translated to combat casualty care for the patient. At the same time, leading civilian investigators were made aware of the needs and current status of the military healthcare system in regards to the care of neurotrauma patients. A variety of topics including trauma biomakers, advanced physiologic monitoring systems, and state-of-the-art imaging systems were discussed and evaluated for their application to combat casualty care of the brain-injured patient during the panel discussions. These discussions provide the basis for the development of collaborative investigations between military physicians and civilian technology developers. AIMBE provided a unique platform which will allow the military a broad range of contacts throughout the medical and engineering disciplines in relevant fields.

AIMBE experts discussed the latest technical advances in the civilian sector for the understanding of brain trauma, post traumatic stress disorder and rehabilitation. TATRC's experts provided perspectives on military needs in these same areas.

Working together, these groups identified during the discussion targets of opportunity in research and clinical settings, and discussed the future of the research.

Topics for further discussion were based on the presentations and include: fMRI access and outcomes; portable field SQUID devices; portable CT use in the field; near infrared imaging; noninvasive ICP; biomarkers-based detection/monitoring; real time acoustic monitoring; neuroprosthetics for rehabilitation; tissue engineering and regenerative medicine CNS; robotics for physical rehabilitation; and fMRI use to monitor rehabilitation.

Each panel discussed the technological value and the challenges of implementing new technology. Each subject area was allotted a one hour panel wherein the topic was discussed from different perspectives: the TATRC speaker discussed what is being done with their area of research; the AIMBE member provided an overview of the subject's current status and direction. After the three specific topic speakers, a panel spoke on the policy implications of the new technology. At the conclusion of each panel, the discussion opened to attendees. The final session of the day was a forty five minute informal conversation between TATRC and the attendees on the topics discussed. The hope is that the attendees will begin to collaborate on the research areas presented.

AIMBE has posted the presentations and summaries on its web-site for access by the engineering community and public where applicable. There are also several journals who may publish the findings from the transcript, namely the *Journal for the International Society for Brain Mapping*, and the meeting was covered in trade publications, including an article in *Military Times* (Appendix F). In future, AIMBE and TATRC will follow-up to create a working group from the attendees and presenters to discuss and share information on topics of mutual interest.

Summary of Presentations

Diffusion Tensor Imaging in Traumatic Brain Injury, Marilyn F. Kraus, Ph.D., Associate Professor of Psychiatry, and Neurology, University of Illinois at Chicago

The Use of Portable Field SQUID Devices; Mark S. Cohen, Ph.D., Professor in Residence, University of California, Los Angeles, School of Medicine

CT and its Role in Portable Field MRI: Alisa D. Gean, M.D., Professor of Radiology, Neurology and Neurological Surgery, University of California, San Francisco; Chief of Neuroradiology, San Francisco General Hospital

Study of Cerebral Functioning with Near Infrared ; Andreas H. Hielscher, Ph.D., Associate Professor of Biomedical Engineering, Columbia University

Challenges and New Devices for Noninvasive ICP Monitoring: R. Daniel Ferguson, Principle Research Scientist, Physical Sciences, Inc.

Use of Biomarkers to Assess Cerebral Status; David Hovda, Ph.D., Professor of Surgery, University of California, Los Angeles

Real Time (Acoustic) Monitoring of the Brain; Richard Dutton, M.D., MBA, Associate Professor of Anesthesiology University of Maryland Medical System

Rehabilitation Therapeutics: The Current State of Technology and Challenges; Lieutenant Colonel Paul F. Pasquina, M.D., Session Chair, Chairman, Physical Medicine & Rehabilitation, Walter Reed Army Medical Center

The Development of Neuroprosthetics in Rehabilitation; Nitish Thakor, Ph.D., Professor of Biomedical Engineering, Johns Hopkins University

Tissue Engineering and Regenerative Medicine CNS as an approach to Rehabilitation; Smita Savant-Bhonsale, Ph.D., Vice President and General Manager, Theradigm, Inc.

Use of Robotics for Physical Rehabilitation; Jacob Rosen, Ph.D., Research Associate Professor, University of Washington

Use of fMRI to Assess Brain Function during Rehabilitation; Scott Frey, Ph.D., Director of the Lewis Center for Neuroimaging, University of Oregon

Expert panel members were as follows:

Seong K. Mun, Ph.D., Director and Professor of Radiology

Director of the Imaging Science and Information System (ISIS) Research Center Georgetown University Medical Center

Ron Kikinis, M.D., Director of the Surgical Planning Laboratory, Professor of Radiology, Harvard Medical School

Larry Clarke, Ph.D., Cancer Imaging Program, National Cancer Institute

Ronald Hayes, Ph.D., Chief Clinical Programs Officer, Founder, Banyan Biomarkers

David Moore, M.D., Ph.D., Director of Research Defense and Veterans Injury, Walter Reed Army Medical Center

Pierre Mourad, Ph.D., Adjunct Professor University of Washington
Colonel Mary Lopez, Chief, Army Occupational Therapy, Assistant Professor,

Center for Ergonomics and Human Performance at Uniformed Services

Joel Myklebust, Ph.D, Director, Division of Physics, Food and Drug Administration

Joseph Pancrazio, Ph.D., Program Director , Extramural Research Program, NIH National Institute of Neurological Disorders and Stroke

The meeting was co-chaired by:

Kenneth C. Curley, M.D., Chief Scientist, US Army Medical Research and Materiel Command Telemedicine and Advanced Technology Research Center

Warren Grundfest, M.D., F.A.C.S., Professor, University of California, Los Angeles

Geoffrey Ling, M.D., Ph.D., Program Manager, Defense Advanced Projects Agency

Key Research Accomplishments

The main goal of this meeting was to exchange information between civilian and military researchers rather than present new research findings. AIMBE believes this was accomplished during the panel discussions and general question and answer periods included at the end of each topic area. A full transcript is attached as an addendum (Appendix B). Full presentations made available to AIMBE have been posted to AIMBE's website, www.aimbe.org, and are also included in the addendum.

Reportable Outcomes

- Speaker Presentations (Appendix A)
- Transcript of discussion (Appendix B)
- Press Release (Appendix C)
- Program document (Appendix D)
- List of Attendees (Appendix E)
- Coverage in *Military Times* (Appendix F)
- Possible Journal Articles

Conclusions

The meeting was a successful first step at bringing together military and civilian leaders to discuss state of the art technologies benefiting the health of the soldiers in the field and to the public in general. Challenges to implementing new technologies were discussed from both a policy and technical perspective.

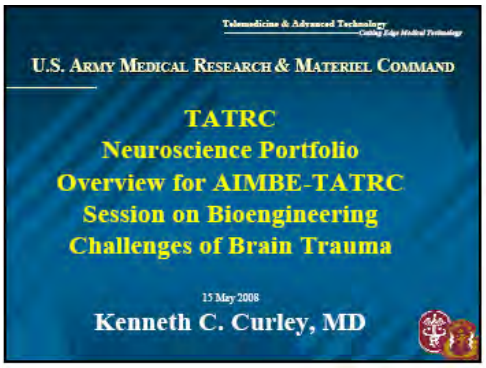
AIMBE plans to develop a working group to collaborate with TATRC on new technologies from participants in this meeting, allowing information, when appropriate and relevant, to be shared by both organizations. As the leading organization representing the medical and biological engineering community, AIMBE believes it is our duty to provide expertise and share information with TATRC about the technologies beneficial to both organizations.

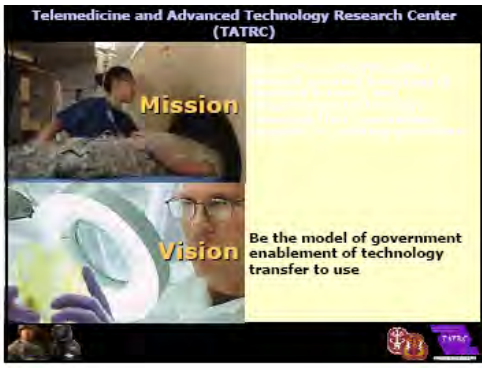
It is our hope AIMBE may host future meetings where new technologies benefiting the public and the military may be discussed. It is important to share best practices and the latest technological advancements to ensure research in development is useful and beneficial all who may be in need.

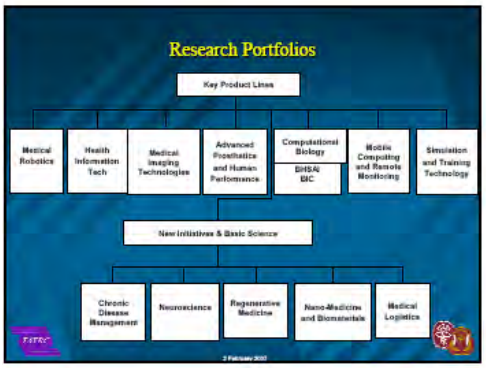
Appendices

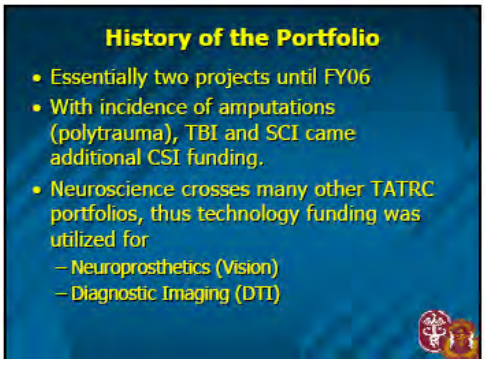
Appendix A
Speaker Presentations

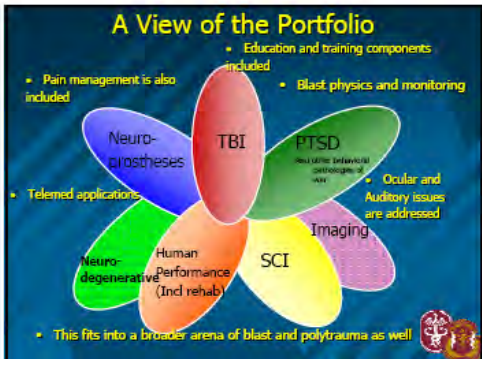
Kenneth C. Curley, M.D.
Meeting Co-Chair
Chief Scientist, U.S. Army Medical Research and Materiel Command (USAMRMC)
Telemedicine and Advanced Technologies Research Center (TATRC)









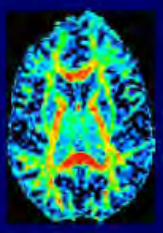


Diffusion Tensor Imaging in Traumatic Brain Injury

Marilyn F. Kraus, Ph.D.
Associate Professor of Psychiatry and Neurology, University of Illinois at Chicago

center for cognitive medicine

University of Illinois at Chicago Departments of Psychiatry and Neurology



Diffusion Tensor Imaging in Traumatic Brain Injury

Bioengineering Challenges of Brain Trauma
AIMBE-Military Collaboration:
February 20, 2008

Marilyn F Kraus, MD
Associate Professor
University of Illinois at Chicago
Departments of Psychiatry and Neurology

diffuse axonal injury (DAI)

- Also referred to as traumatic axonal injury (TAI)
- Can occur *without* direct impact to the head
- progressive pathophysiologic *process* initiated primarily by acceleration-deceleration forces, aka impulsive loading (Ommaya and Gennarelli 1974)

DAI in TBI

- DAI may be the only significant pathology found in certain cases of TBI, and has been identified via direct pathological studies as well as neuroimaging even in mild TBI
  - (Povlishock et al., 1983; Graham et al., 1989; Blumbergs et al., 1994; Goodman, 1994; Mittl et al., 1994; Aihara et al., 1995; Blumbergs et al., 1995; Gennarelli, 1996; Inglese et al., 2005b; Kraus et al 2007).
- WM lesions have been reported in various areas in different studies, may vary with methods, acuity and severity of population studied.

diffusion tensor imaging (DTI)

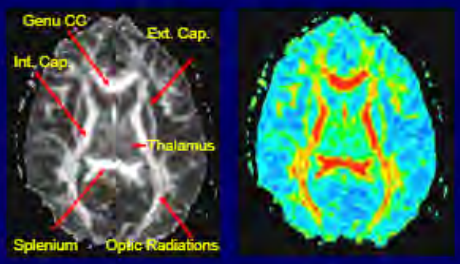
- DTI allows for specific examination of integrity of white matter tracts.
- DTI is a modification of diffusion–weighted imaging. The difference is that you calculate the *tensor* in DTI. (Basser and others - development and implementation of a tensor model).
- DTI is based upon the diffusivity of water molecules, which is variably restricted in different tissues.
- In WM, diffusivity is more restricted -more anisotropic

fractional anisotropy (FA)

- FA – the fraction of the magnitude of D that is due to anisotropic diffusivity.
- Values range from 0 to 1 where 0 represents isotropic diffusion, or lack of directional organization, and 1 represents anisotropic diffusion, or organized tissues such as in WM tracts.
- FA -information as to the shape of the diffusion tensor at each voxel.
- FA – can be used to assess the integrity of the white matter tract in question

Diffusion Tensor Imaging (DTI) -FA Maps

Fractional Anisotropy Maps



AIMBE report to USAMRMC-TATRC Award #: W81XWH-08-1-0125
AIMBE- Military Collaboration: Bioengineering Challenges of Brain Trauma Conference on February 20, 2008

White Matter Integrity and cognition in Chronic Traumatic Brain Injury: A Diffusion Tensor Imaging Study

Marilyn F. Kraus, Teresa Susmaras, Benjamin P. Caughlin, Corey J. Walker, John A. Sweeney, and Deborah M. Little

Departments of Psychiatry, Neurology, Psychology, Bioengineering, Anatomy, Ophthalmology, Center for Cognitive Medicine, and Center for Stroke Research

Kraus MF et al. Brain October 2007

methods overview:

37 TBI subjects - 20 mild, 17 moderate to severe chronic TBI subjects (minimum 6 months out from injury; average time out 107 months). Relatively strict inclusion exclusion.

18 healthy matched controls (age, education)

DTI -Fractional anisotropy (FA), axial and radial diffusivity were calculated from the DTI data. FA was the primary measure of white matter integrity. A Region of interest (ROI) analysis was done.

Neuropsychological testing - Cognitive domain scores were calculated from executive, attention, and memory testing.

DTI data acquisition

- 3.0-Tesla whole body scanner (Signa VHi, GE Medical Systems) using a customized DTI pulse sequence with a quadrature head coil.
- sequence based on single-shot EPI pulse sequence. diffusion gradient directions = 27, TR = 5200ms, TE = minimum (81ms), b-values = 0, 750 s/mm2, FOV = 22cm, Matrix = 132x132 (reconstructed to 256x256, slice thickness = 5mm, gap = 1.5mm, ramp-sampling = on, NEX = 2, total acquisition time = 5:46.
- Additional 3D high resolution anatomical scan acquired -3D inversion recovery fast spoiled gradient recalled (3D IRfSPGR)
- The 28 diffusion directions (with B0 image) used to calculate FA. Images reconstructed and FA, λ1, λ2 and λ3 calculated using DTI Studio. FA, λ1, λ2, and λ3 were converted to ANALYZE format and read into SPM2 for analysis.

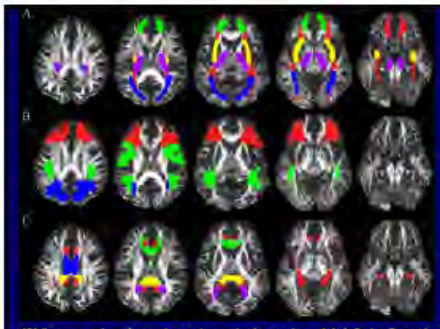


Figure 1. Example of ROI masks

(A) forceps minor (green), cortico-spinal tract (purple), inferior fronal-occipital fasciculus (red), external capsule (yellow), sagittal stratum (blue)
(B) anterior corona radiata (green), superior longitudinal fasciculus (red), posterior corona radiata (blue);
(C) cingulum (red), corpus callosum body (blue), splenium (yellow), and genu (green), and forceps major (purple).

Results of ROI analysis

- Mod/sev TBI group- decreased FA was found in all 13 ROIs
- Mild TBI group – reduced FA was significant in 3 ROIs - cortico-spinal tract, sagittal stratum, and superior longitudinal fasciculus.

Note: To ensure that FA was only calculated from white matter tissue, a threshold of 0.20 was applied prior to extraction of individual subjects' FA maps.

white matter load

- index of global white matter integrity = number of ROIs with decreased FA values compared to controls (may be more sensitive to WM abnormalities by looking at the actual number of affected areas across the brain independent of individual variability in the specific location of these abnormalities).
- z-scores were calculated for the FA within each ROI. Control group mean and standard deviation were treated as zero. Abnormal FA – defined as FA ≥ 1 SD below control mean.

Results:

- controls- M=3.61, SEM=0.55
- mild TBI- M=5.9, SEM=0.72
- M/STBI- M=9.05, SEM=0.89

Differences were significant

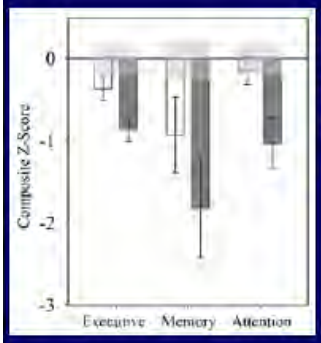


Figure 2. Mean domain scores (normalized z-scores) for the MTBI (white) and MSTBI (dark gray). Note -light gray box around zero indicates 1SEM around the control mean.

-impairments in all 3 domains found for the moderate/severe group. While not statistically significant, the mild TBI group showed trends.

correlations of WML and cognition

- significant correlations were found between the *executive* and *memory domains* with the white matter load.
- The correlation with the *attention* domain was not significant.

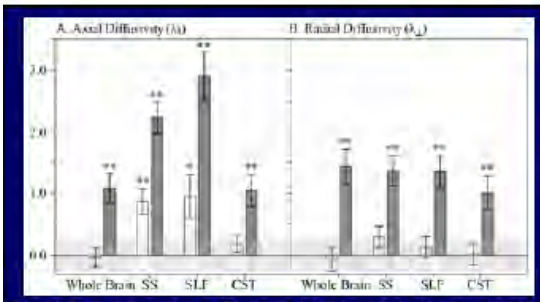


*Figure 4. Mean normalized axial (λ∥) and radial (λ⊥) diffusivity for the mild TBI (white) and MSTBI (dark gray). * p<0.05, ** p<.01. The light gray box around zero indicates 1SEM around the control mean. SS= sagittal stratum, SLF =superior longitudinal fasciculus, CST= corticospinal tract.*

The Role of DTI- Questions

- What is current role of DTI in TBI?
  - Currently, being done clinically but precision varies
  - Goal of research- a standardized clinical methodology for assessment, prognosis and treatment planning
  - Role in differentiating etiologies of symptoms? For example, in possible PTSD (or other psychiatric condition) versus mild TBI. Correct diagnosis has significant implications for treatment
- How does DTI compare with MRI, functional MRI?
  - Structural MRI alone- not as useful for WM as DTI
  - fMRI- *functional* information.
- Future Directions
  - High Resolution DTI
  - Role in researching blast injury

acknowledgements

The TBI Lab

- Deborah Little
- Teresa Susmaras
- Benjamin P. Caughlin
- Corey Walker
- Eric Van Raay
- Narina Simonian

- John Sweeney
- Neil Pliskin
- Joe Zhou
- Harvey Levin

DTI- methods overview

- A device, the Gradient (pulsed magnetic field gradient) is used to sensitize MRI signal intensity to amount of H20 diffusion (D). It induces LINEAR magnetic field inhomogeneity along the direction of the gradient
- The *strength and polarity* of the gradient is controlled, and can be turned on and off.
- The Gradient pulses change the SIGNAL FREQUENCY based on LOCATION of the H20.
- This occurs because the magnetic field is kept as homogenous as possible (B0) so that the H20 molecules resonate at equivalent frequencies. The application of the gradient causes the H20 at different locations to resonate at different frequencies
- This is the primary difference between DTI and MRI - *Unlike standard structural MRI, the homogeneity of the magnetic field is varied in a linear fashion by gradients*

Demographics

	Control		MTBI		M/STBI		All	Control vs	Control vs
	M	SEM	M	SEM	M	SEM	Groups	MTBI	M/STBI
Age	32.83	2.51	35.85	2.10	34.88	2.82	0.673	0.360	0.590
Years Education	16.76	0.44	16.55	0.53	15.47	0.77	0.276	0.763	0.154
WTAR Premorbid IQ Estimate	113.24	1.80	112.65	2.43	106.59	2.60	0.100	0.852	0.043*
Time from Injury (in months)			92.55	18.61	124.35	23.12	0.286		
Age at Time of Injury (years)			29.00	2.37	24.50	2.51	0.199		
Length of LOC (hours)			0.11	0.05	237.00	111.50	0.042*		

Gender: TBI – 21 females; 16 males Controls – 11 female; 7 males

Region of Interest (ROI) analyses

- ROI analyses carried out on individual data and hand-drawn in standardized space. ROIs were drawn individually on the FA maps with respect to the T2 FSE and color-coded FA maps.
- ROIs included (13): anterior and posterior corona radiata (respectively, ACR and PCR), cortico-spinal tracts (CST) which included parts of the cortico-pontine tract and parts of the superior thalamic radiation, cingulum fibers (CG), forceps minor (fMin), forceps major (fMaj), the body, genu, and splenium of the corpus callosum (bCC, gCC, and sCC), the inferior frontooccipital fasciculus (IFO), the superior longitudinal fasciculus (SLF), external capsule (ExCap) and the sagittal stratum including the optic radiations (SS).

DTI Data Analysis

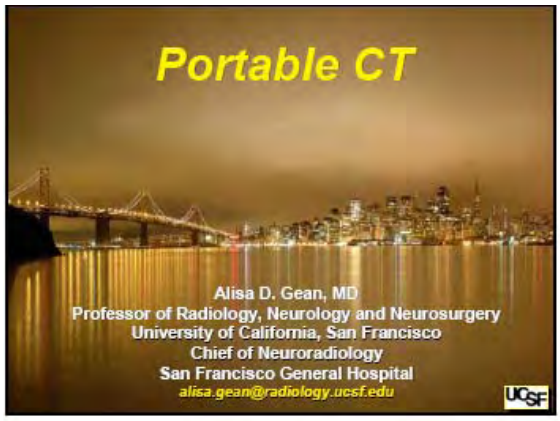
- The 28 diffusion directions, including the B0 image, were used to calculate the fractional anisotropy (FA). The images were reconstructed and FA, λ1, λ2 and λ3 were calculated using the program from Johns Hopkins, DTI Studio (Wakana et al., 2004).
- Head movement was required to be within one voxel across the image acquisition. Noise can introduce bias in estimates of the eigenvalues and because noise decreases the signal-to-noise ratio, so we applied a background noise level to all subjects prior to calculation of pixel-wise FA and the eigenvalues (λ1, λ2, λ3) (background noise = 125).
- The FA, λ1, λ2, and λ3 were converted to ANALYZE format and read into SPM2 (Statistical Parametric Mapping) software for analysis. Data from each subject was co-registered with their corresponding T1 weighted anatomic image set (after skull stripping) using a normalized mutual information cost function and trilinear interpolation. Normalization parameters were determined based upon the high resolution T1 image relative to MNI template. These normalization parameters were then applied to the FA and eigenvalue images. Each image was visually checked for accuracy after both the co-registration and normalization steps.
- From these eigenvalue maps, axial (λ‖ = λ1) and radial (λ⊥=(λ2+ λ3)/2) diffusivity were calculated. Although no additional smoothing was applied to the data the magnitude of spatial filtering which occurs during normalization to standardized space can potentially affect the DTI data (see Jones et al., 2005; Smith et al., 2006). In some cases, large smoothing kernels can potentially reduce group differences (Jones et al., 2005).

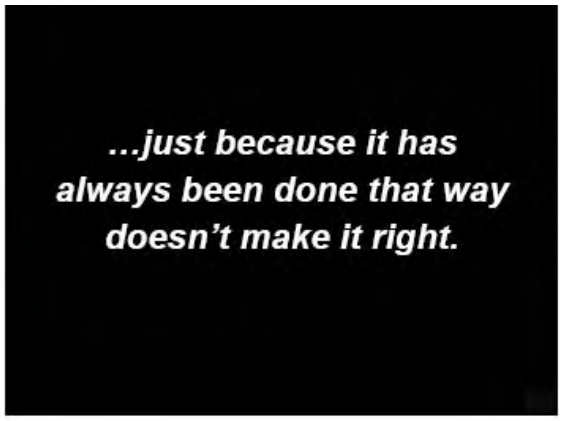
Statistics

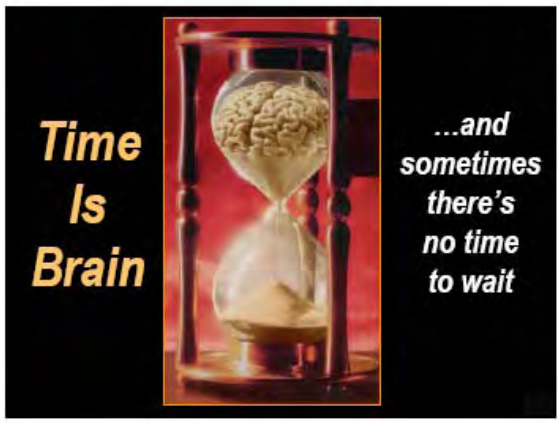
- Neuropsychological test scores analyzed using one-way ANOVA with group membership (controls, MTBI, M/STBI) and were corrected for multiple comparisons using the least significant difference post-hoc tests. The primary measures of interest were 3 domain scores-executive, memory and attention domains. Correlations with FA done using bivariate Pearson correlations.
- DTI data- The primary analyses carried out on the dependent measures extracted from the DTI data was a two-way mixed design ANOVA with cerebral hemisphere (right, left) as the within subjects comparison and group membership (controls, MTBI and M/STBI) as the between subjects comparison. For those regions where areas in both hemispheres were assessed together (corpus callosum and cerebral peduncles) the analysis was a one-way between subjects ANOVA with group membership (controls, MTBI and M/STBI) as the between subjects comparison. The primary dependent measure was fractional anisotropy (FA). Data were confirmed to have a normal distribution using the Kolmogorov-Smirnov test.

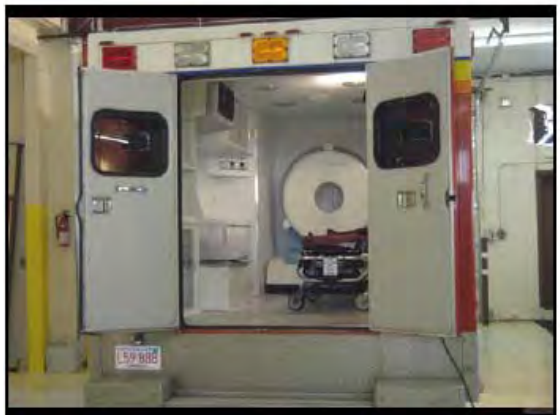
Portable CT Use in Evaluating TBI in the Field

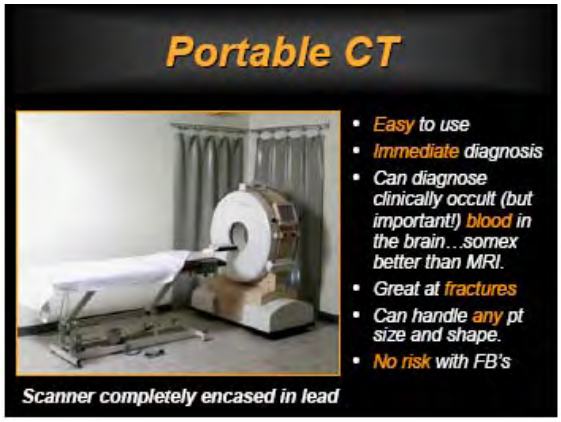
Alisa D. Gean, M.D.
Professor of Radiology, Neurology and Neurological Surgery, University of California, San Francisco,
Chief of Neuroradiology, San Francisco General Hospital



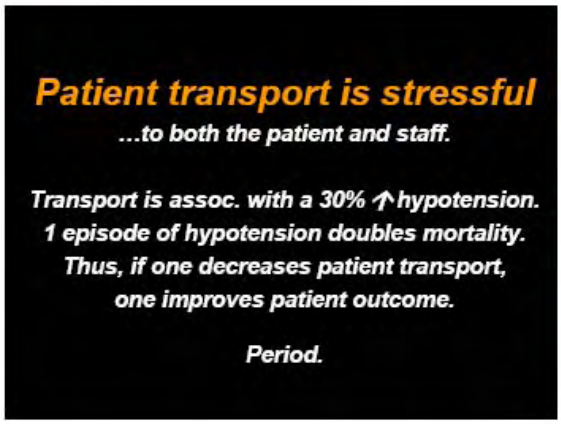


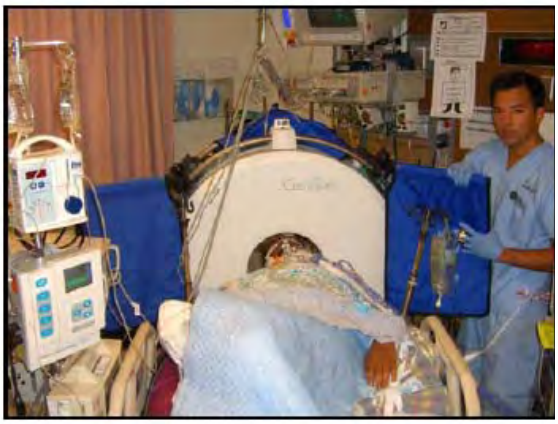


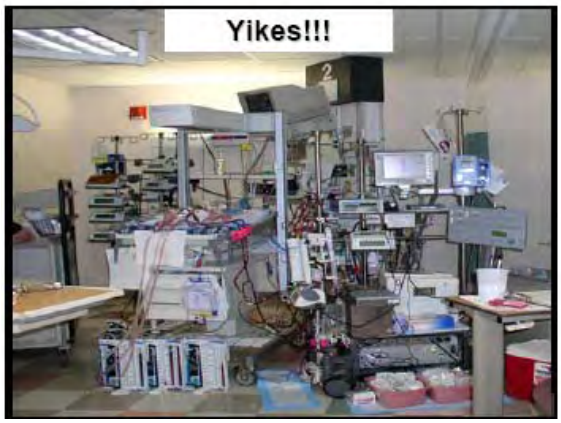



Portable CT
Easy to use
Immediate diagnosis
Can diagnose clinically occult (but important!) blood in the brain…somex better than MRI.
Great at fractures
Can handle any pt size and shape.
No risk with FB's
Scanner completely encased in lead

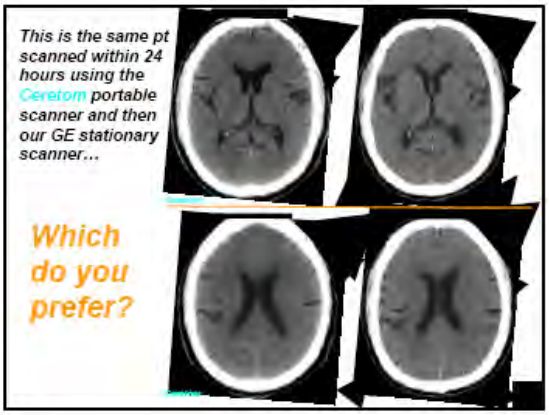

Advanced Neuromonitoring in the ICU
External ventricular Drainage catheter (EVD)
Brain Tissue Oxygen Monitor
Jugular venous saturation catheter
Endotracheal tube (ETT)
Feeding tube
Arterial line
Venous line (insulin, IVF, versed, fentanyl)
Potential cervical spine injury

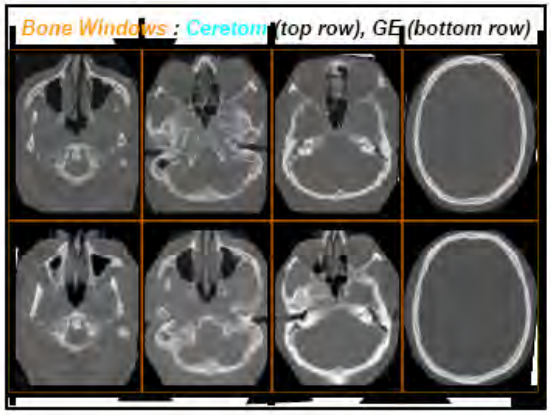

Patient transport is stressful
…to both the patient and staff.
Transport is assoc. with a 30% ↑ hypotension.
1 episode of hypotension doubles mortality.
Thus, if one decreases patient transport,
one improves patient outcome.
Period.

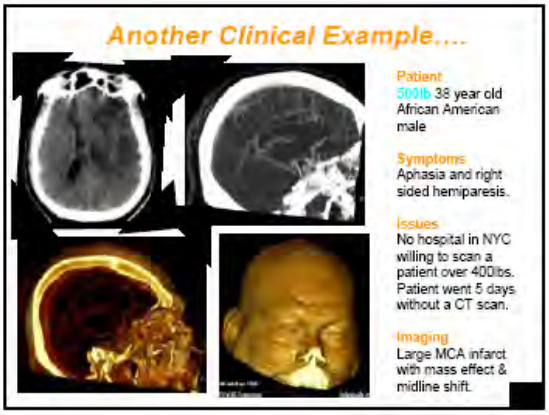


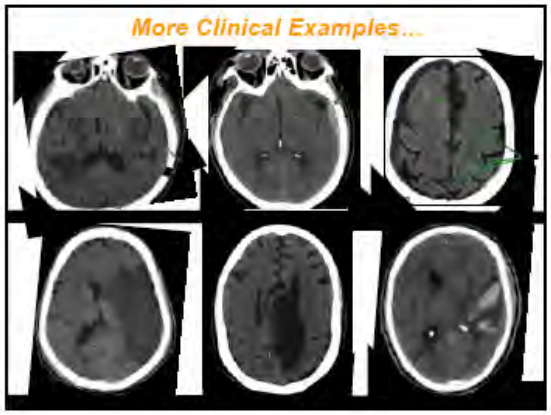

Yikes!!!

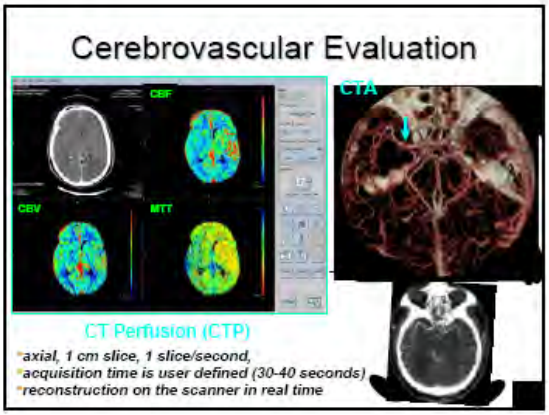

How good are the images?

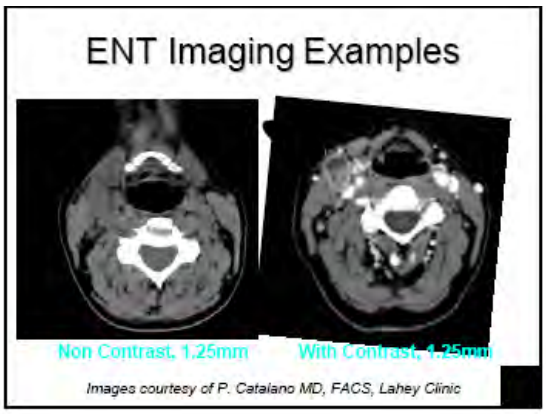

This is the same pt scanned within 24 hours using the Ceretom portable scanner and then our GE stationary scanner…
Which do you prefer?

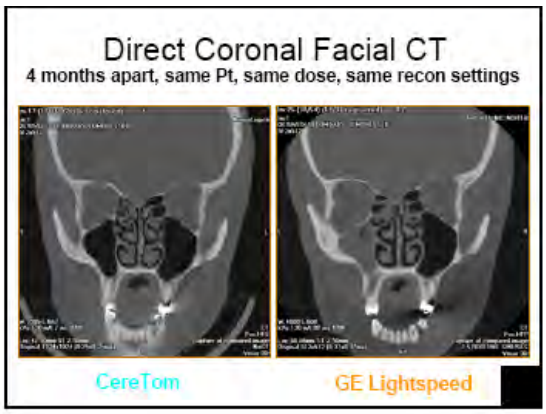

Bone Windows : Ceretom (top row), GE (bottom row)


Another Clinical Example….
Patient
500lb 38 year old African American male
Symptoms
Aphasia and right sided hemiparesis.
Issues
No hospital in NYC willing to scan a patient over 400lbs. Patient went 5 days without a CT scan.
Imaging
Large MCA infarct with mass effect & midline shift.

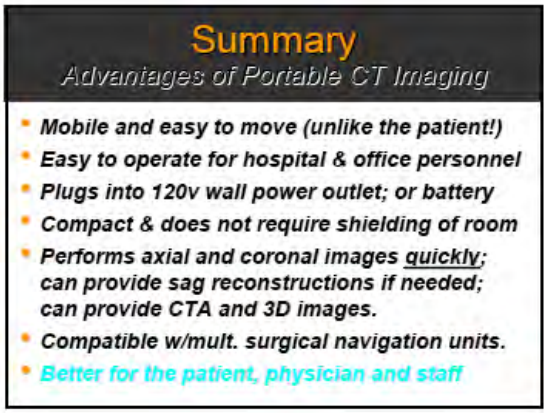

More Clinical Examples…


Cerebrovascular Evaluation
CBF
CBV
MTT
CTA
CT Perfusion (CTP)
*axial, 1 cm slice, 1 slice/second,
*acquisition time is user defined (30-40 seconds)
*reconstruction on the scanner in real time

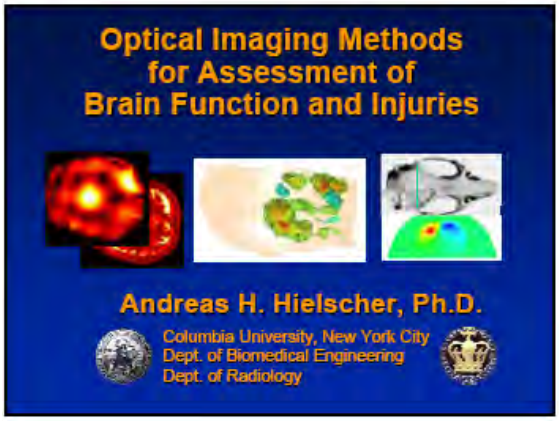

ENT Imaging Examples
Non Contrast, 1.25mm
With Contrast, 1.25mm
Images courtesy of P. Catalano MD, FACS, Lahey Clinic

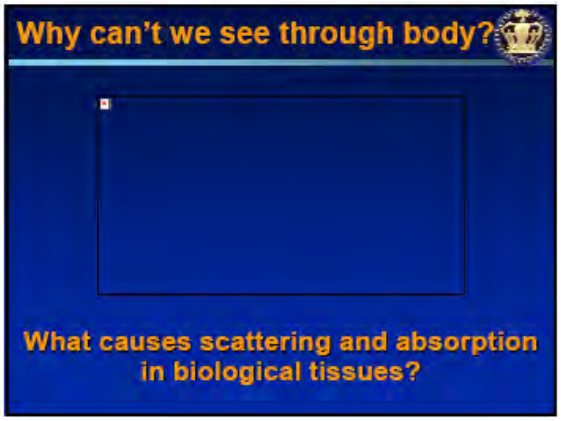

Direct Coronal Facial CT
4 months apart, same Pt, same dose, same recon settings
CereTom
GE Lightspeed

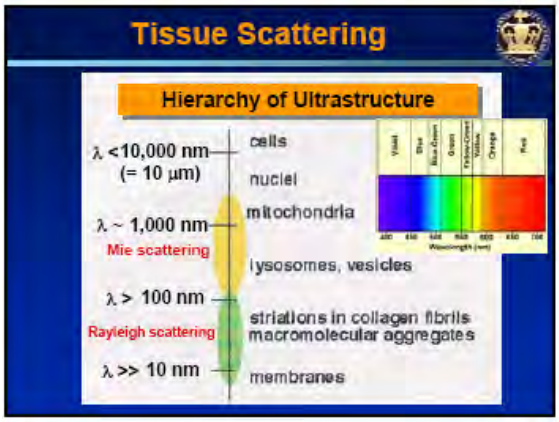

Direct coronal imaging

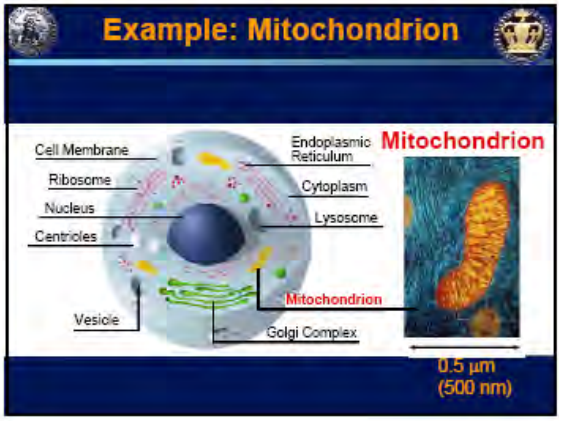

Summary
Advantages of Portable CT Imaging
Mobile and easy to move (unlike the patient!)
Easy to operate for hospital & office personnel
Plugs into 120v wall power outlet; or battery
Compact & does not require shielding of room
Performs axial and coronal images quickly; can provide sag reconstructions if needed; can provide CTA and 3D images.
Compatible w/mult. surgical navigation units.
Better for the patient, physician and staff

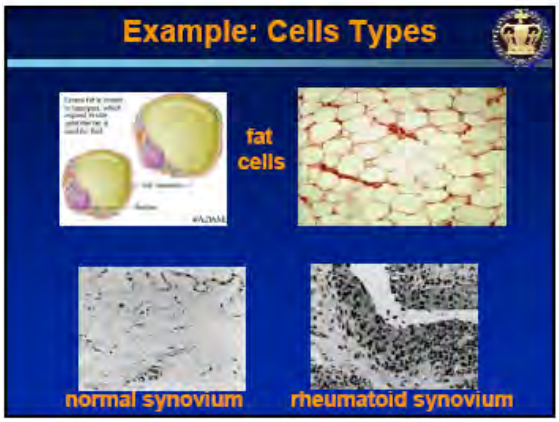

Thank You!
alisa.gean@radiology.ucsf.edu


Optical Imaging Methods
for Assessment of
Brain Function and Injuries
Andreas H. Hielscher, Ph.D.
Columbia University, New York City
Dept. of Biomedical Engineering
Dept. of Radiology


Why can't we see through body?
What causes scattering and absorption
in biological tissues?

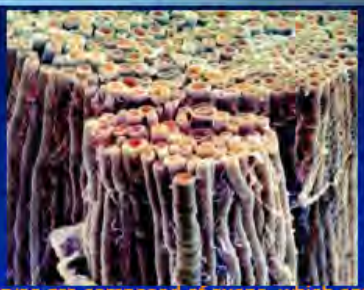

Tissue Scattering
Hierarchy of Ultrastructure
λ <10,000 nm
(= 10 μm)
cells
nuclei
mitochondria
λ ~ 1,000 nm
Mie scattering
lysosomes, vesicles
λ > 100 nm
striations in collagen fibrils
macromolecular aggregates
Rayleigh scattering
λ >> 10 nm
membranes


Example: Mitochondrion
Cell Membrane
Ribosome
Nucleus
Centricles
Endoplasmic
Reticulum
Cytoplasm
Lysosome
Mitochondrion
Vesicle
Golgi Complex
Mitochondrion
0.5 μm
(500 nm)


Example: Cells Types
fat
cells
normal synovium
rheumatoid synovium


Collagen Fibrils
• Collagen fibers are 2 – 3 microns in diameter
and composed of smaller collagen fibrils
about 0.3 microns in diameter

Nerves



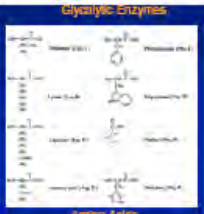
- Nerves are composed of axons, which can range from ~0.1 to 10 microns in diameter

Tissue Absorption

Everything absorbs light !

Chemical structures of the 5 nitrogen-containing ring compounds: purines and pyrimidines bases (A, G, U,T, and C) in nucleic acids.

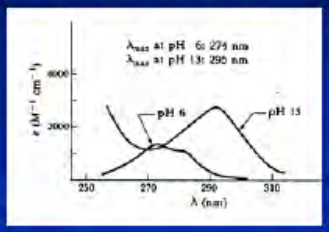
Glycolytic Enzymes



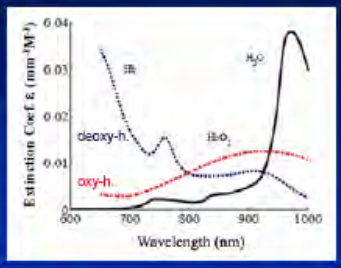
Amino Acids

Example : Tyrosine Spectrum

The absorption spectrum of the amino acid Tyrosine is pH dependent!



Important Example : Hemoglobin



Metal porphyrin ring system is mainly responsible for the color in heme proteins. (Why is finger red?)

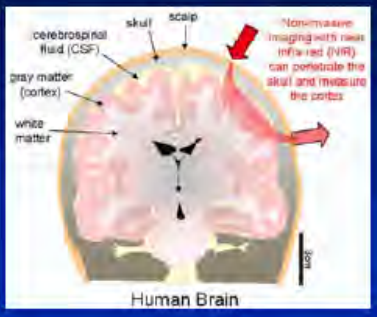
Two Wavelengths

Measurements provide absorption μ_a for each wavelength.

$$\mu_a^{\lambda 1} = \varepsilon_{Hb}^{\lambda 1}\,[Hb] + \varepsilon_{HbO_2}^{\lambda 1}[HbO_2]$$
$$\mu_a^{\lambda 2} = \varepsilon_{Hb}^{\lambda 2}\,[Hb] + \varepsilon_{HbO_2}^{\lambda 2}[HbO_2]$$

$$[Hb] = \frac{\varepsilon_{HbO_2}^{\lambda 2}\mu_a^{\lambda 1} - \varepsilon_{HbO_2}^{\lambda 1}\mu_a^{\lambda 2}}{\varepsilon_{Hb}^{\lambda 1}\,\varepsilon_{HbO_2}^{\lambda 2} - \varepsilon_{Hb}^{\lambda 2}\,\varepsilon_{HbO_2}^{\lambda 1}}$$
$$[HbO_2] = \frac{\varepsilon_{Hb}^{\lambda 1}\mu_a^{\lambda 2} - \varepsilon_{Hb}^{\lambda 2}\mu_a^{\lambda 1}}{\varepsilon_{Hb}^{\lambda 1}\,\varepsilon_{HbO_2}^{\lambda 2} - \varepsilon_{Hb}^{\lambda 2}\,\varepsilon_{HbO_2}^{\lambda 1}}$$

Brain "Imaging"



Overview

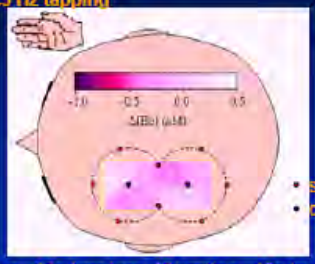
- Topography (NIR - Spectroscopy)
- Tomography
- Instrumentation
- Challenges

Overview

- Topography (NIR - Spectroscopy)
- Tomography
- Instrumentation
- Challenges

Functional Brain Imaging

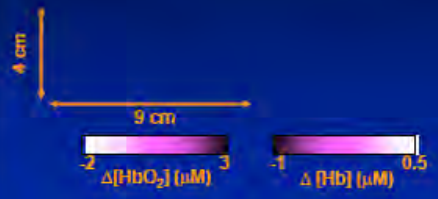
2.5 Hz tapping



17s resting - 10s tapping - 17 resting - 10s tapping ...

Courtesy of M. Franceschini, Tufts University / MGH, Boston, MA

Topographic Mapping of Hemodynamics



courtesy of M. Franceschini, Tufts University / MGH, Boston, MA

Two Wavelengths

Reconstruction algorithm provides $\Delta\mu_a$ for each element (pixel or voxel) for each wavelength.

$$\Delta\mu_a^{\lambda 1} = \varepsilon_{Hb}^{\lambda 1}\,\Delta[Hb] + \varepsilon_{HbO_2}^{\lambda 1}\,\Delta[HbO_2]$$

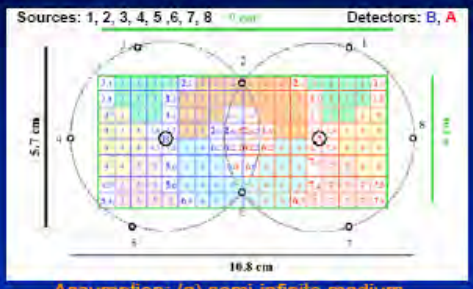
$$\Delta\mu_a^{\lambda 2} = \varepsilon_{Hb}^{\lambda 2}\,\Delta[Hb] + \varepsilon_{HbO_2}^{\lambda 2}\,\Delta[HbO_2]$$

$$\Delta[Hb] = \frac{\varepsilon_{HbO_2}^{\lambda 2}\Delta\mu_a^{\lambda 1} - \varepsilon_{HbO_2}^{\lambda 1}\Delta\mu_a^{\lambda 2}}{\varepsilon_{Hb}^{\lambda 1}\,\varepsilon_{HbO_2}^{\lambda 2} - \varepsilon_{Hb}^{\lambda 2}\,\varepsilon_{HbO_2}^{\lambda 1}}$$

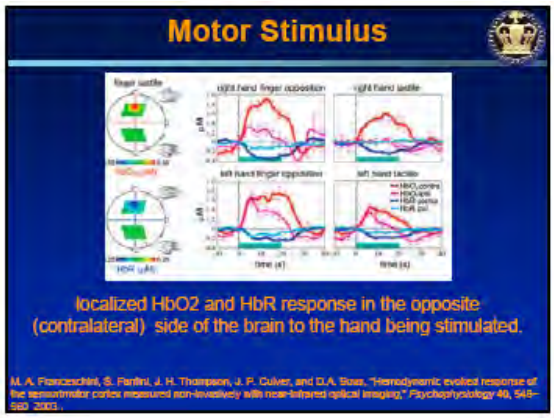
$$\Delta[HbO_2] = \frac{\varepsilon_{Hb}^{\lambda 1}\Delta\mu_a^{\lambda 2} - \varepsilon_{Hb}^{\lambda 2}\Delta\mu_a^{\lambda 1}}{\varepsilon_{Hb}^{\lambda 1}\,\varepsilon_{HbO_2}^{\lambda 2} - \varepsilon_{Hb}^{\lambda 2}\,\varepsilon_{HbO_2}^{\lambda 1}}$$

Measurement of $\Delta\mu_a$ at least 10x more accurate than μ_a !!

Topographic Backprojection



Assumption: (a) semi-infinite medium
(b) constant path-length L


Motor Stimulus
localized HbO2 and HbR response in the opposite (contralateral) side of the brain to the hand being stimulated.


Overview
• Tomography

Goal

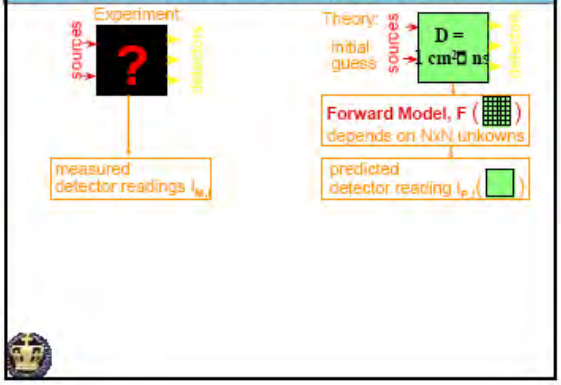
Three-dimensional (volumetric) reconstruction of the distribution of optical properties in the brain from surface measurements using model-based iterative image reconstruction scheme.

Measurement Geometry

λ1 = 760 nm and λ2 = 830nm

Model-Based Iterative Image Reconstruction

Model-Based Iterative Image Reconstruction



Forward Model

3D-Time-Resolved Diffusion Equation

$$\frac{\partial U}{\partial t} = \frac{c}{\partial x} D \frac{\partial U}{\partial x} + \frac{c}{\partial y} D \frac{\partial U}{\partial y} + \frac{c}{\partial z} D \frac{\partial U}{\partial z} - c\mu_a U + S$$

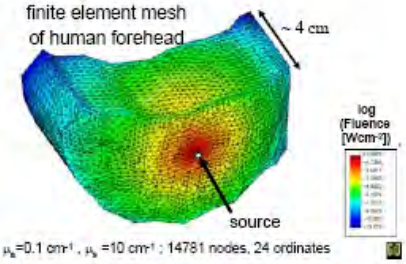
with c := speed of light in medium, S = Source,

and diffusion coefficient : $D = c\,(\,3\,[\,\mu_a + \mu_s'\,]\,)^{-1}$

with μ_a = absorption coefficient and

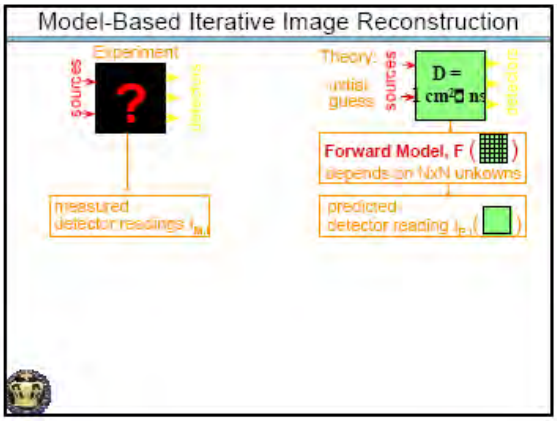
μ_s' = reduced scattering coefficient.

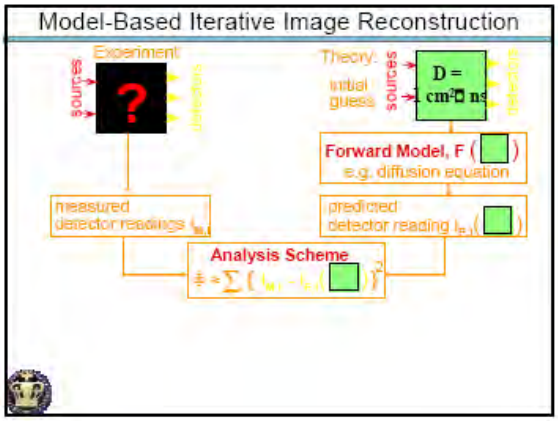
Forward Model

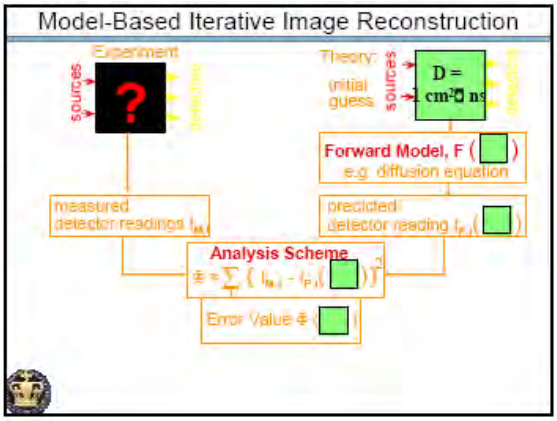


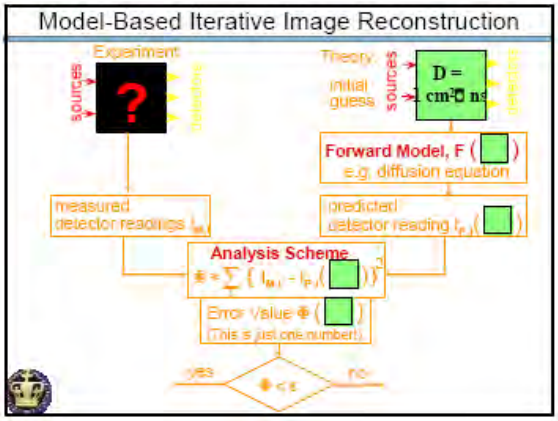
μ_a=0.1 cm⁻¹, μ_s =10 cm⁻¹ ; 14781 nodes, 24 ordinates

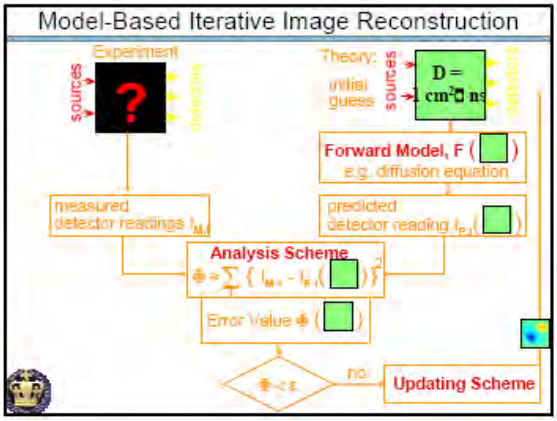
Model light propagation in tissue as function of spatial distribution of absorption, $\mu_a(r)$, and scattering, $\mu_s(r)$.

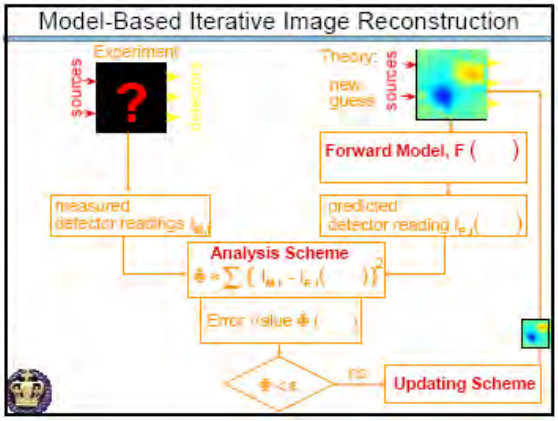

Model-Based Iterative Image Reconstruction
Experiment
sources
detectors
Theory:
initial guess
D =
Forward Model, F
depends on NxN unkowns
measured detector readings
predicted detector reading

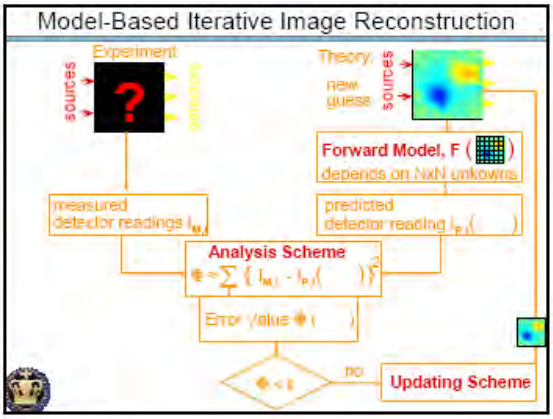

Model-Based Iterative Image Reconstruction
Experiment
sources
detectors
Theory:
initial guess
D =
Forward Model, F
e.g. diffusion equation
measured detector readings
predicted detector reading
Analysis Scheme

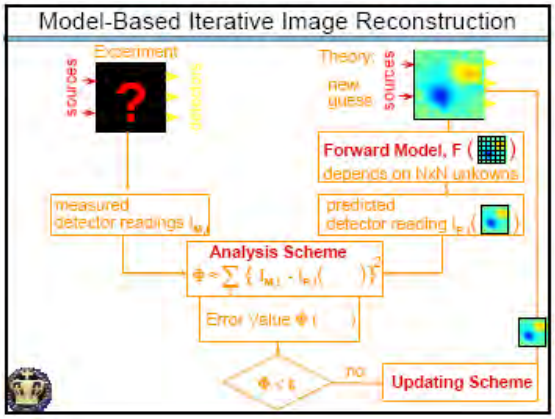

Model-Based Iterative Image Reconstruction
Experiment
sources
detectors
Theory:
initial guess
D =
Forward Model, F
e.g. diffusion equation
measured detector readings
predicted detector reading
Analysis Scheme
Error Value

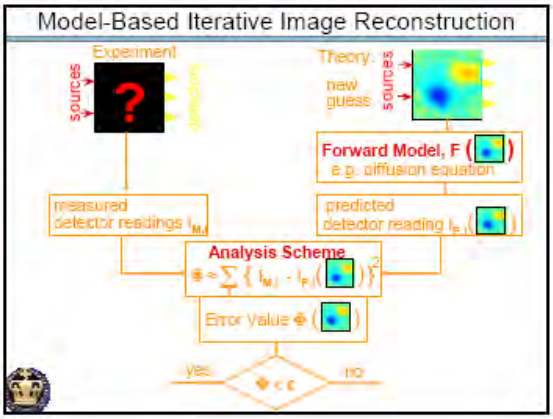

Model-Based Iterative Image Reconstruction
Experiment
sources
detectors
Theory:
initial guess
D =
Forward Model, F
e.g. diffusion equation
measured detector readings
predicted detector reading
Analysis Scheme
Error Value
yes
no

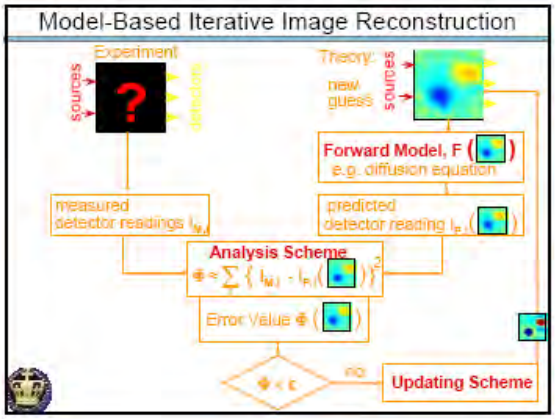

Model-Based Iterative Image Reconstruction
Experiment
sources
detectors
Theory:
initial guess
D =
Forward Model, F
e.g. diffusion equation
measured detector readings
predicted detector reading
Analysis Scheme
Error Value
no
Updating Scheme

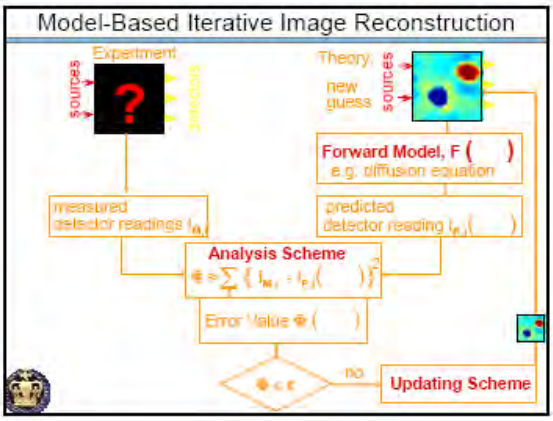

Model-Based Iterative Image Reconstruction
Experiment
sources
detectors
Theory:
new guess
Forward Model, F
measured detector readings
predicted detector reading
Analysis Scheme
Error Value
no
Updating Scheme

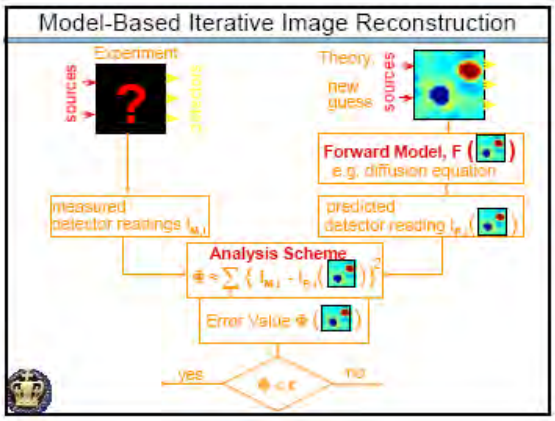

Model-Based Iterative Image Reconstruction
Experiment
sources
detectors
Theory:
new guess
sources
Forward Model, F ( )
depends on NxN unkowns
measured detector readings
predicted detector reading
Analysis Scheme
Error Value
no
Updating Scheme

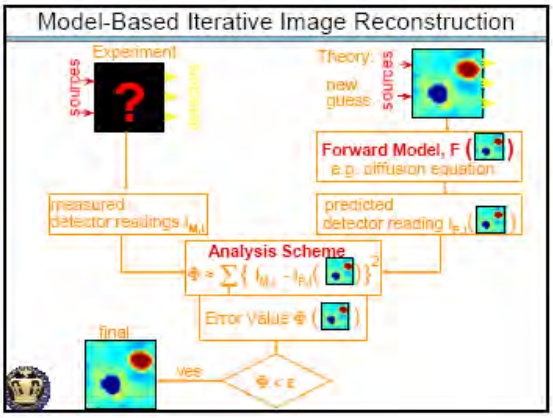

Model-Based Iterative Image Reconstruction
Experiment
sources
detectors
Theory:
new guess
sources
Forward Model, F ( )
depends on NxN unkowns
measured detector readings
predicted detector reading
Analysis Scheme
Error Value
no
Updating Scheme

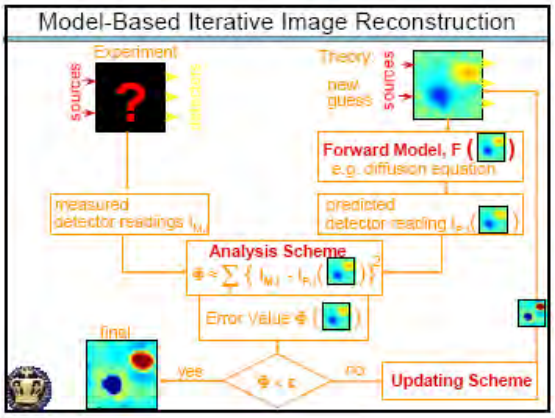

Model-Based Iterative Image Reconstruction
Experiment
sources
detectors
Theory:
new guess
sources
Forward Model, F ( )
e.g. diffusion equation
measured detector readings
predicted detector reading
Analysis Scheme
Error Value
yes
no

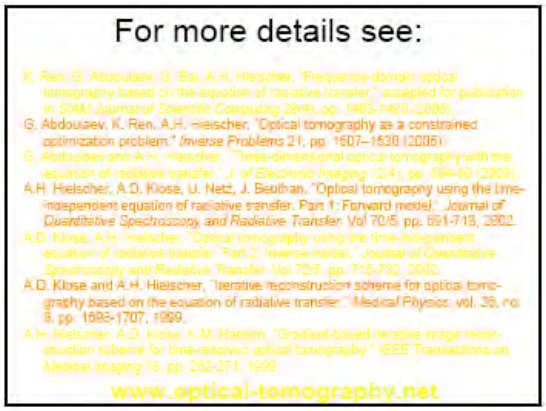

Model-Based Iterative Image Reconstruction
Experiment
sources
detectors
Theory:
new guess
sources
Forward Model, F ( )
e.g. diffusion equation
measured detector readings
predicted detector reading
Analysis Scheme
Error Value
no
Updating Scheme

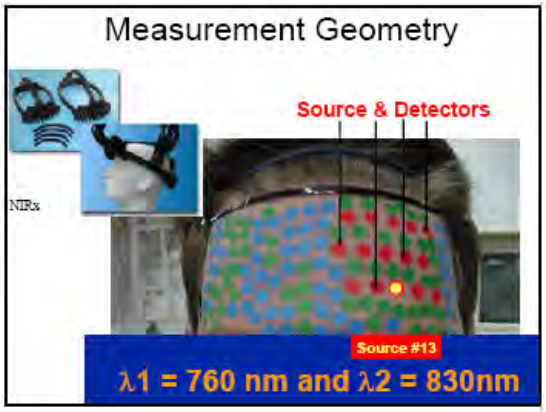

Model-Based Iterative Image Reconstruction
Experiment
sources
detectors
Theory:
new guess
sources
Forward Model, F ( )
e.g. diffusion equation
measured detector readings
predicted detector reading
Analysis Scheme
Error Value
no
Updating Scheme

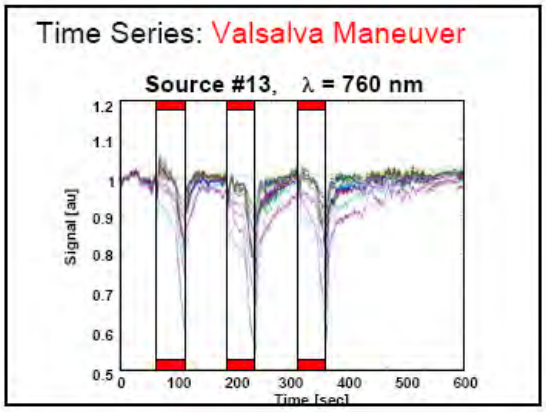

Model-Based Iterative Image Reconstruction
Experiment
sources
detectors
Theory:
new guess
sources
Forward Model, F ( )
e.g. diffusion equation
measured detector readings
predicted detector reading
Analysis Scheme
Error Value
yes
no

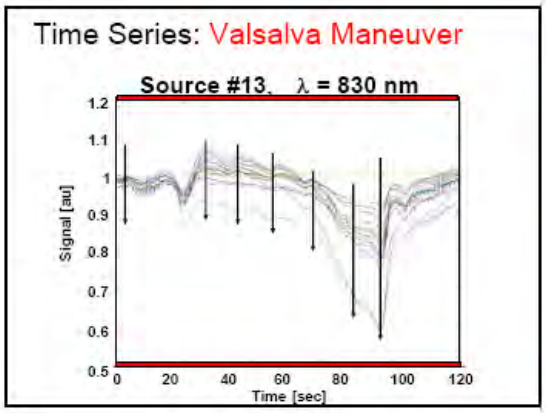

Model-Based Iterative Image Reconstruction
Experiment
sources
detectors
Theory
new guess
sources
Forward Model, F
e.g. diffusion equation
measured detector readings
predicted detector reading
Analysis Scheme
Error Value
final
yes

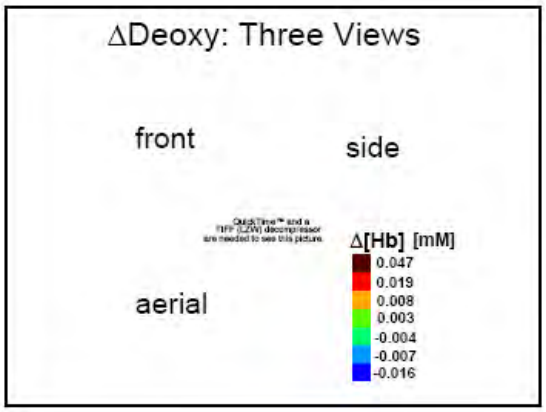

Model-Based Iterative Image Reconstruction
Experiment
sources
detectors
Theory
new guess
sources
Forward Model, F
e.g. diffusion equation
measured detector readings
predicted detector reading
Analysis Scheme
Error Value
final
yes
no
Updating Scheme

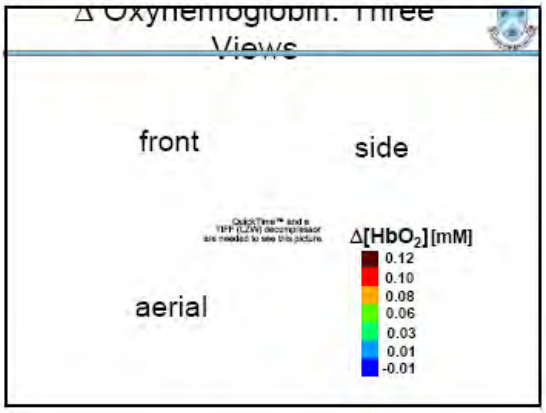

For more details see:
K. Ren, G. Abdoulaev, G. Bal, A.H. Hielscher, "Frequency-domain optical tomography based on the equation of radiative transfer," accepted for publication in SIAM Journal of Scientific Computing 28(4), pp. 1463-1489 (2006).
G. Abdoulaev, K. Ren, A.H. Hielscher, "Optical tomography as a constrained optimization problem," Inverse Problems 21, pp. 1507–1530 (2005).
G. Abdoulaev and A.H. Hielscher, "Three-dimensional optical tomography with the equation of radiative transfer," J. of Electronic Imaging 12(4), pp. 594-601 (2003).
A.H. Hielscher, A.D. Klose, U. Netz, J. Beuthan, "Optical tomography using the time-independent equation of radiative transfer. Part 1: Forward model," Journal of Quantitative Spectroscopy and Radiative Transfer, Vol 70/5, pp. 691-713, 2002.
A.D. Klose, A.H. Hielscher, "Optical tomography using the time-independent equation of radiative transfer. Part 2: Inverse model," Journal of Quantitative Spectroscopy and Radiative Transfer, Vol 72/5, pp. 715-732, 2002.
A.D. Klose and A.H. Hielscher, "Iterative reconstruction scheme for optical tomography based on the equation of radiative transfer," Medical Physics, vol. 35, no. 8, pp. 1693-1707, 1999.
A.H. Hielscher, A.D. Klose, K.M. Hanson, "Gradient-based iterative image reconstruction scheme for time-resolved optical tomography," IEEE Transactions on Medical Imaging 18, pp. 262-271, 1999.
www.optical-tomography.net

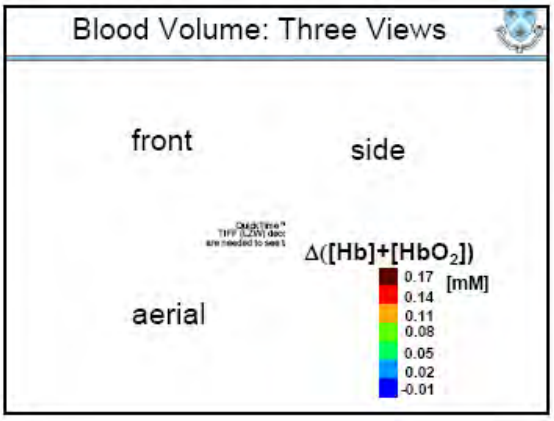

Measurement Geometry
Source & Detectors
NIRx
Source #13
λ1 = 760 nm and λ2 = 830nm

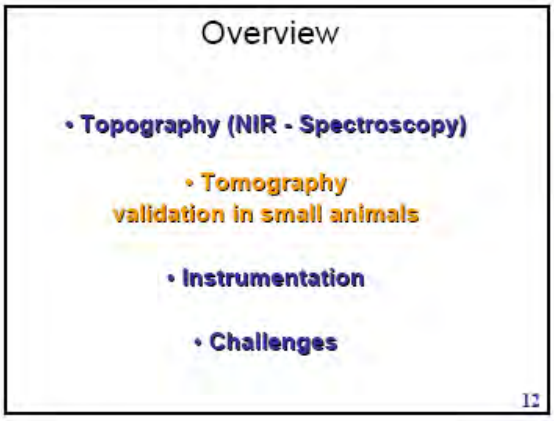

Time Series: Valsalva Maneuver
Source #13, λ = 760 nm
Signal [au]
Time [sec]

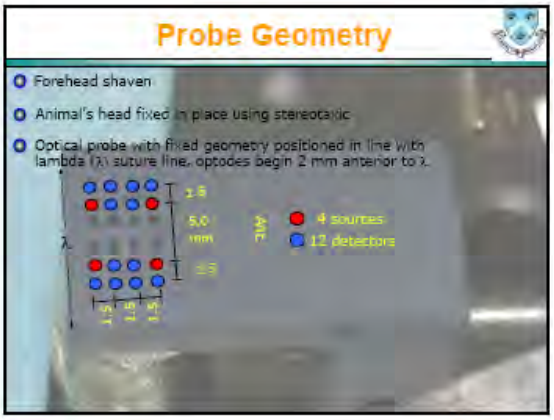

Time Series: Valsalva Maneuver
Source #13, λ = 830 nm
Signal [au]
Time [sec]

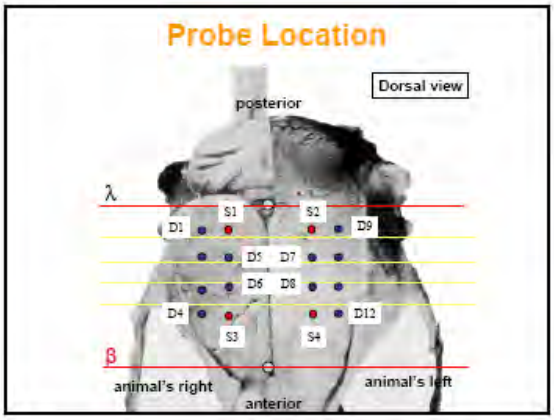

ΔDeoxy: Three Views
front
side
aerial
Δ[Hb] [mM]
0.047
0.019
0.008
0.003
-0.004
-0.007
-0.016

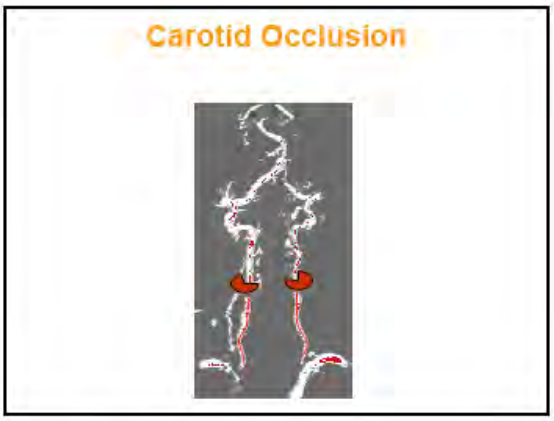

front
side
aerial
Δ[HbO2] [mM]
0.12
0.10
0.08
0.06
0.03
0.01
-0.01

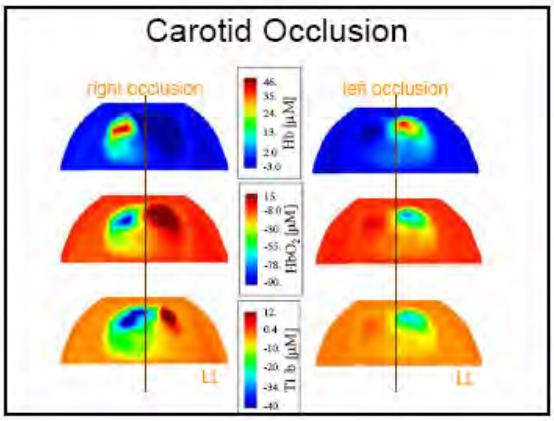

Blood Volume: Three Views
front
side
aerial
Δ([Hb]+[HbO2])
0.17
0.14
0.11
0.08
0.05
0.02
-0.01
[mM]

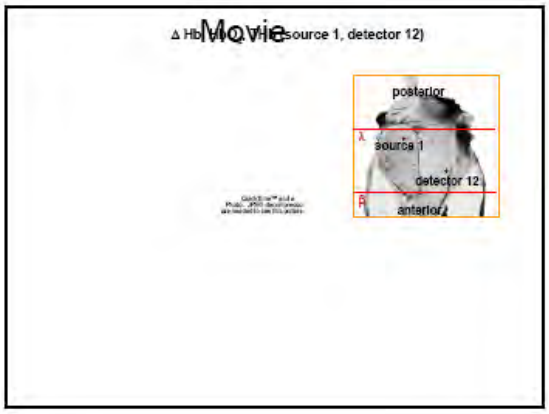

Overview
• Topography (NIR - Spectroscopy)
• Tomography
validation in small animals
• Instrumentation
• Challenges
12

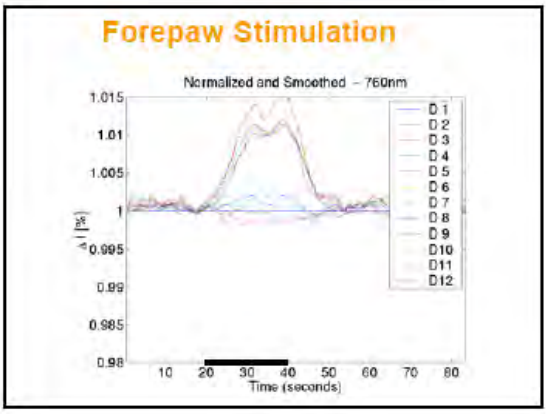

Probe Geometry
Forehead shaven
Animal's head fixed in place using stereotaxic
Optical probe with fixed geometry positioned in line with lambda (λ) suture line, optodes begin 2 mm anterior to λ
4 sources
12 detectors

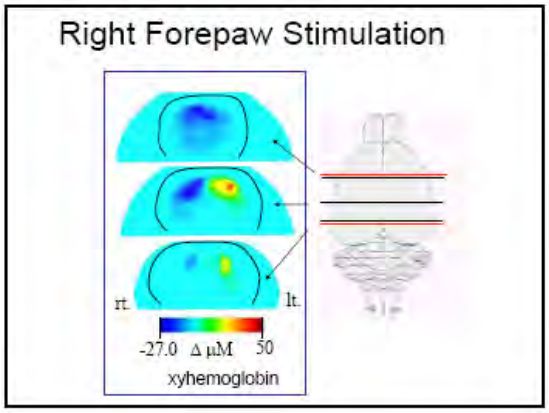

Probe Location
Dorsal view
posterior
λ
S1
S2
D1
D9
D5
D7
D6
D8
D4
D12
S3
S4
β
animal's right
anterior
animal's left

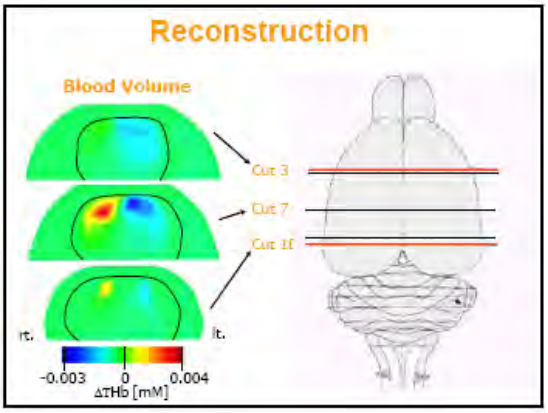

Carotid Occlusion

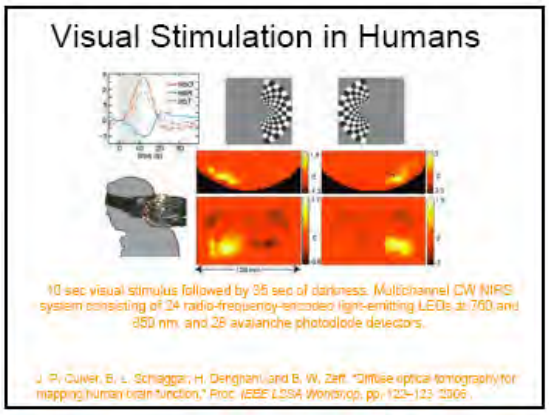

Carotid Occlusion
right occlusion
left occlusion
Hb [μM]
HbO2 [μM]
Ti b [μM]

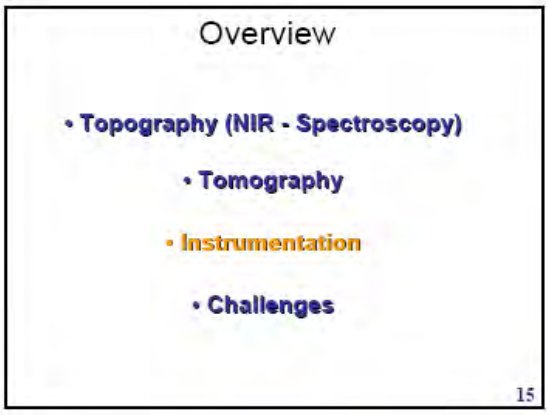

Movie
Δ Hb (Source 1, detector 12)
posterior
source 1
detector 12
anterior

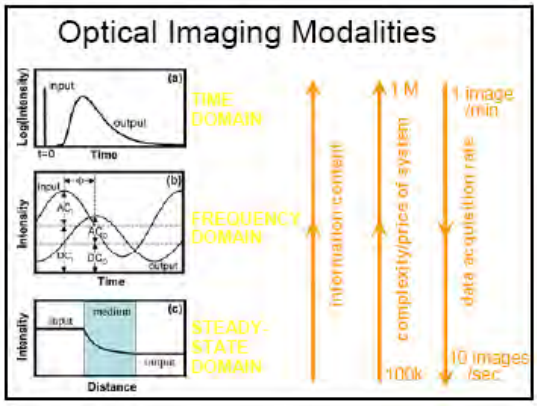

Forepaw Stimulation
Normalized and Smoothed – 760nm
1.015
1.01
1.005
1
0.995
0.99
0.985
0.98
Δ I [%]
10 20 30 40 50 60 70 80
Time (seconds)
D 1
D 2
D 3
D 4
D 5
D 6
D 7
D 8
D 9
D10
D11
D12

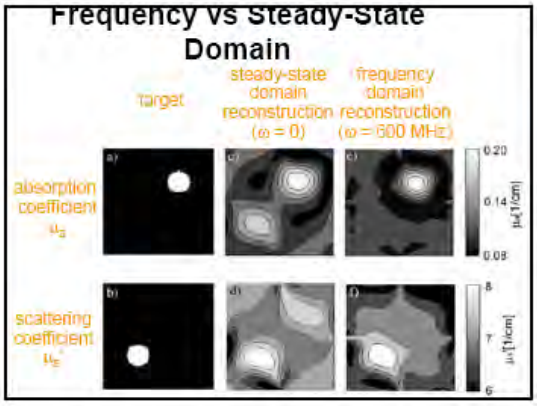

Right Forepaw Stimulation
rt.
lt.
-27.0 Δ μM 50
xyhemoglobin


Reconstruction
Blood Volume
Cut 3
Cut 7
Cut 11
rt.
lt.
-0.003 0 0.004
ΔTHb [mM]

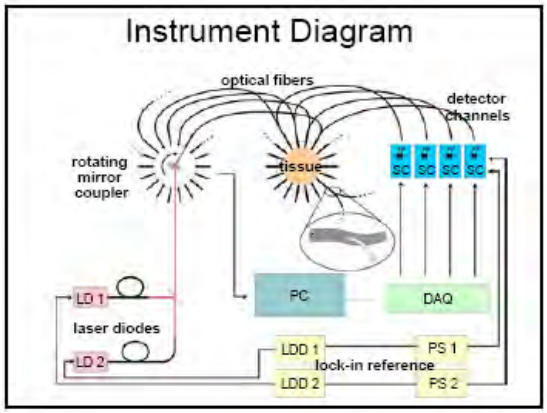

Visual Stimulation in Humans
10 sec visual stimulus followed by 35 sec of darkness. Multichannel CW NIRS system consisting of 24 radio-frequency-encoded light-emitting LEDs at 760 and 850 nm, and 28 avalanche photodiode detectors.
J. P. Culver, B. L. Schlaggar, H. Dehghani, and B. W. Zeff, "Diffuse optical tomography for mapping human brain function," Proc. IEEE LEOS Workshop, pp. 123–123, 2006.

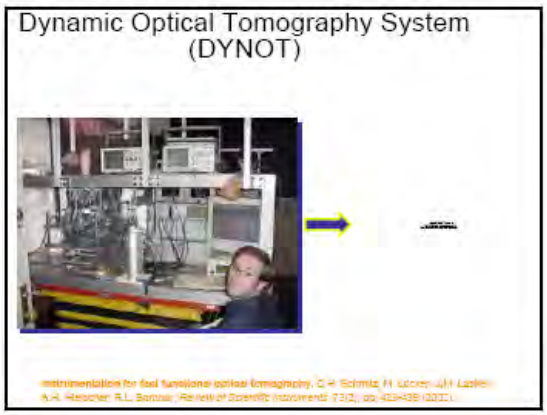

Overview
• Topography (NIR - Spectroscopy)
• Tomography
• Instrumentation
• Challenges
15

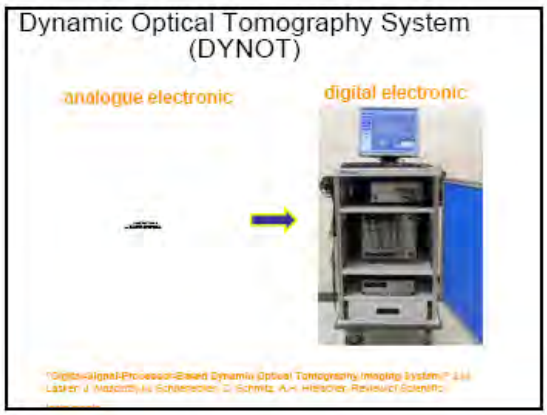

Optical Imaging Modalities
TIME DOMAIN
FREQUENCY DOMAIN
STEADY-STATE DOMAIN
information content
complexity/price of system
data acquisition rate
1 M
100k
1 image /min
10 images /sec

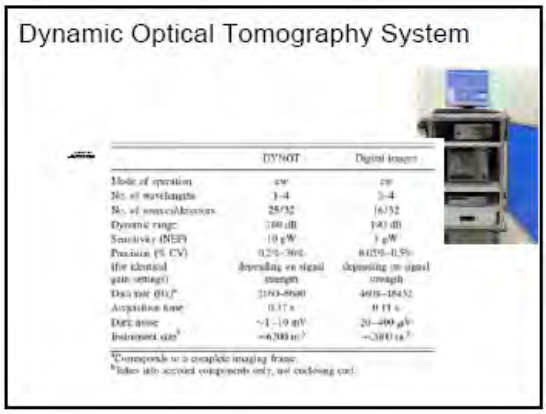

Frequency vs Steady-State Domain
Target
steady-state domain reconstruction (ω = 0)
frequency domain reconstruction (ω = 600 MHz)
absorption coefficient
scattering coefficient

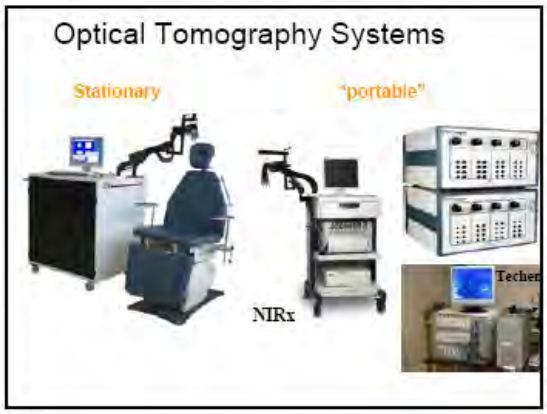

Dynamic Optical Tomography System
(DYNOT)
Amp
Opto-deMUX
Up to 10 full tomographic images per second!


Instrument Diagram
optical fibers
detector channels
rotating mirror coupler
tissue
SC
PC
DAQ
LD 1
laser diodes
LD 2
LDD 1
LDD 2
lock-in reference
PS 1
PS 2


Dynamic Optical Tomography System
(DYNOT)


Dynamic Optical Tomography System
(DYNOT)
analogue electronic
digital electronic


Dynamic Optical Tomography System
DYNOT


Optical Tomography Systems
Stationary
"portable"
NIRx

Handheld Probes

"The preoperative accuracy of NIRS in detecting the hematoma existence was same as the accuracy of the radiologic imaging but the postoperative findings were not reliable. The sensitivity of the device in detecting abnormality was found to be 0.87 … (There were 11 acute, 1 subacute, and 18 chronic hematomas … The device diagnosed all acute hematomas)

S. Kahraman, H. Kayali, C. Atabey, F. Acar, and S. Gocmen, "The accuracy of near-infrared spectroscopy in detection of subdural and epidural hematomas," J. Trauma 61(6), 1480–1483, 2006

Challenges & Opportunities

CHALLENGES:

- **Motion artifacts**
- **Speed of reconstruction algorithms**
- **Absolute values of hemodynamic parameters**

OPPORTUNITIES

- **Hybrid Systems**
- **Fluorescence Imaging**

18

Acknowledgements

- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS - RO1 AR46255-01 PI: Hielscher)
- National Institute for Biomedical Imaging and Bioengineering (NIBIB - R01 EB001900-01 PI: Hielscher)
- National Cancer Institute (NCI 1R21CA118666-01A2: PI: Hielscher)
- NCI - U54CA126513; Tumor Microenvironment Research Network PI: Wang; Imaging Core PI: Hielscher
- New York State Office of Science, Technology and Academic Research - Technology Transfer Incentive Program (NYSTAR-TTIP - PI: Hielscher)

More Information

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

www.optical-tomography.net

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T. Brown (Radiology, Columbia University)
H. Liu (Biomedical Eng., University of Texas - Arlington)
R.L. Barbour (SUNY Downstate Medical Center)
C. Schmitz (NIRx Medical Technologies, Inc.)

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S. He

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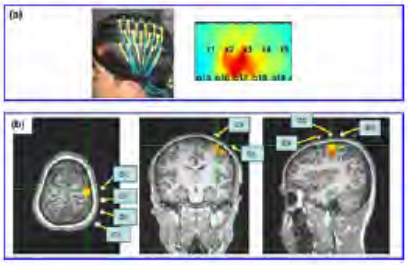
X. Gu
A. Klose, Ph.D.
G. Abdoulaev, Ph.D.

END

EXTRAS

MRI-Optical Hybrid Systems

MRI-Optical Hybrid Imaging

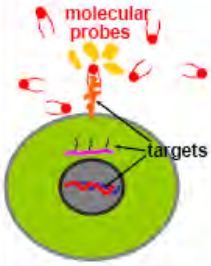


Combine high resolution of MRI with speed and versatility of optical methods.

EXTRAS

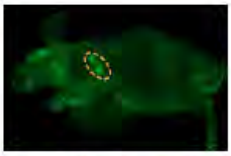
Fluorescence Imaging

Fluorescent Probes



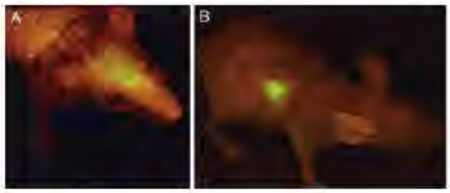
upon excitation with external light source

green fluorescent protein (GFP)



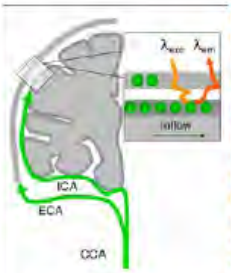
Using GFP and its derivatives it is possible to visualize nearly any protein of interest in any cell, tissue, or species. (single-molecule dynamics, protein trafficking within cells, organelle dynamics, and cell and tissue behaviors during development, cancer progression)

Green Fluorescent Protein (GFP)



Imaging of vAD-GFP gene expression in the brain and liver (72 hours after gene delivery)

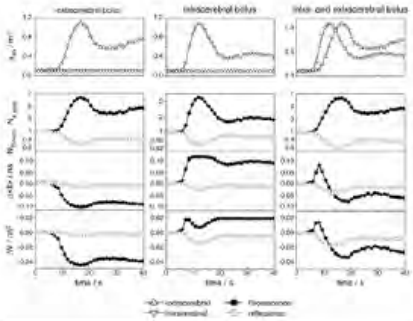
Fluorescence Imaging



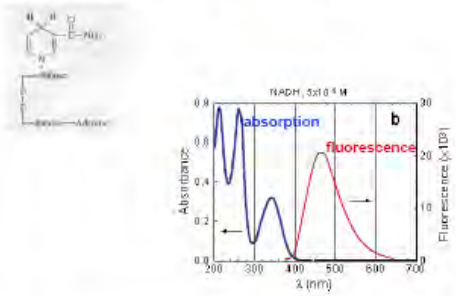
First report on results proving that fluorescence of exogenous dyes inside the human brain can be excited and detected non-invasively at the surface of the adult head.

Faster blood flow in the intra-cerebral artery (ICA) leads to an earlier arrival of indocyanine green (ICG) in the brain when compared to the extracerebral tissue, which is exclusively fed by the extracerebral artery (ECA).

Fluorescence Imaging



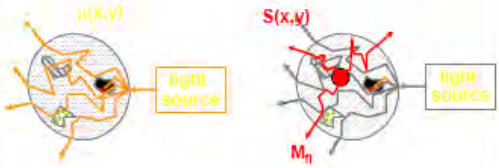
Example: NADH



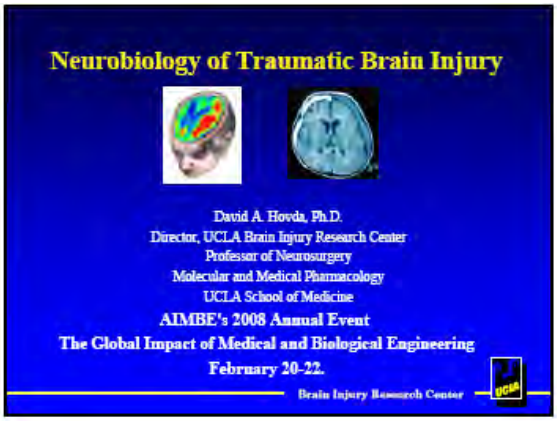
Fluorescence Tomography

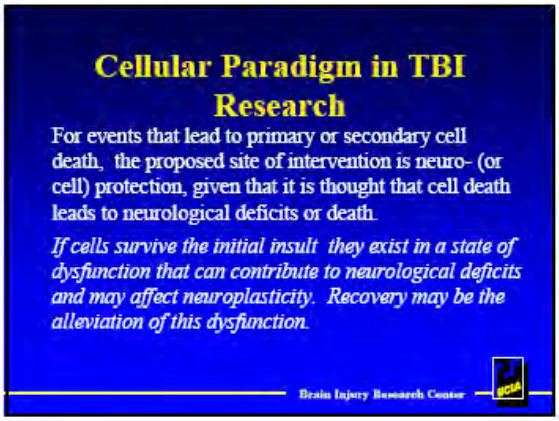
reconstruction of absorption and scattering profile $\mu(x,y)$

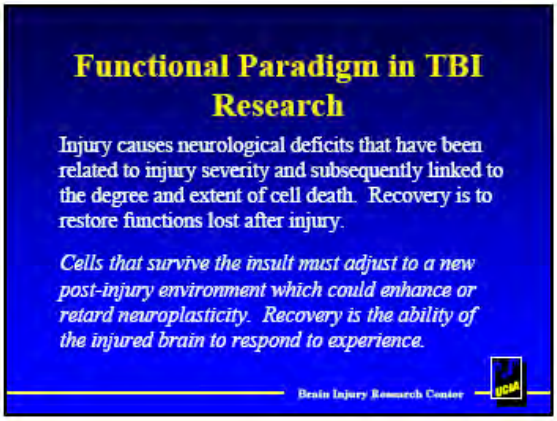
reconstruction of fluorescence source profile **S(x,y)**

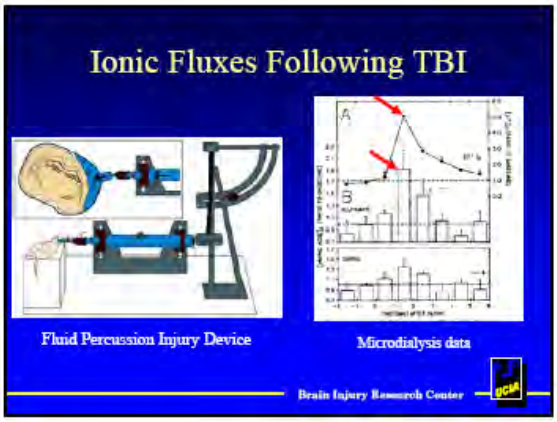


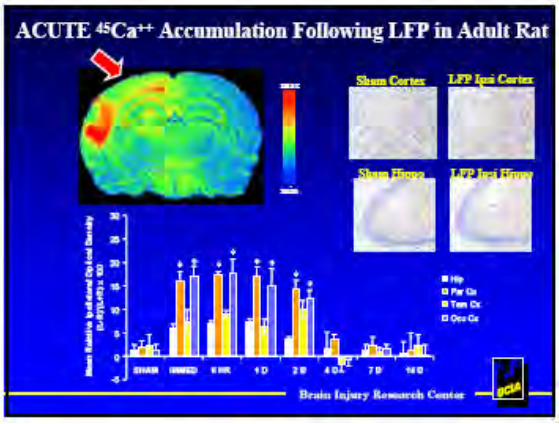
Use of Biomarkers to Assess Cerebral Status
David Hovda, Ph.D.
Professor of Surgery, University of California, Los Angeles

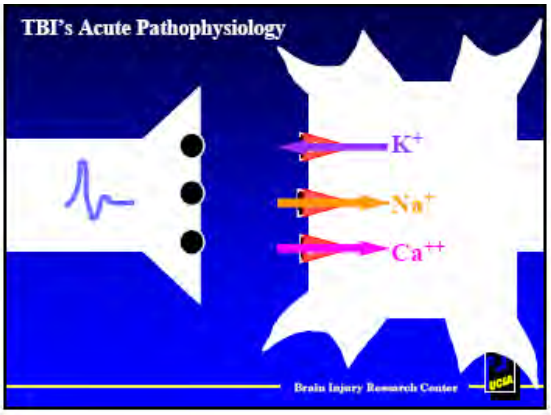


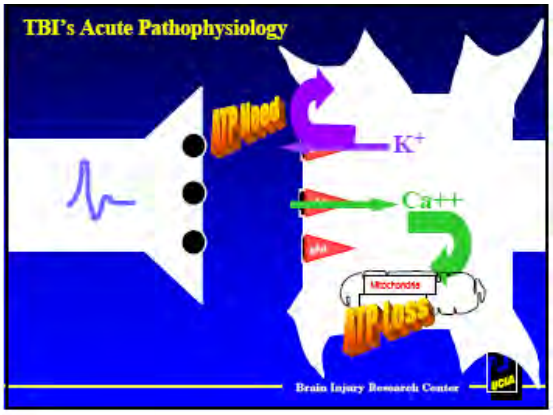


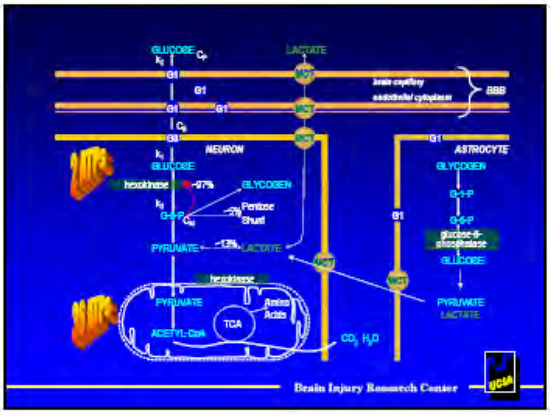


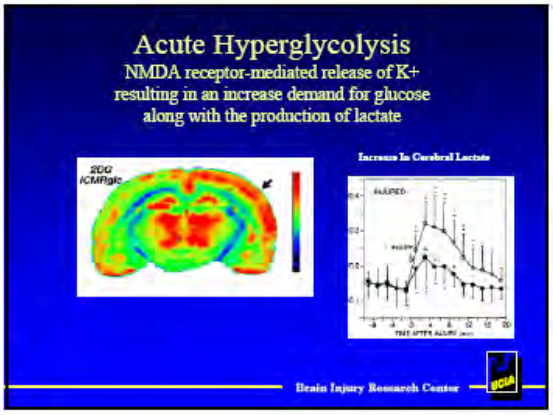


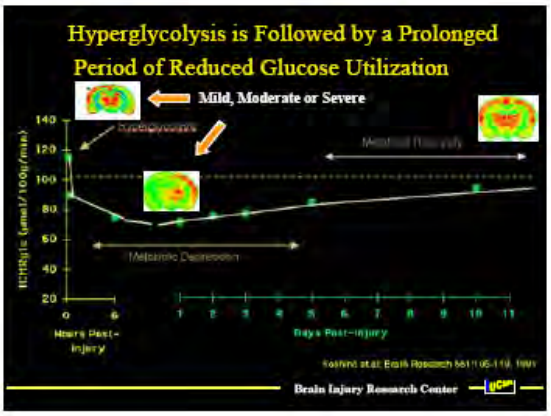


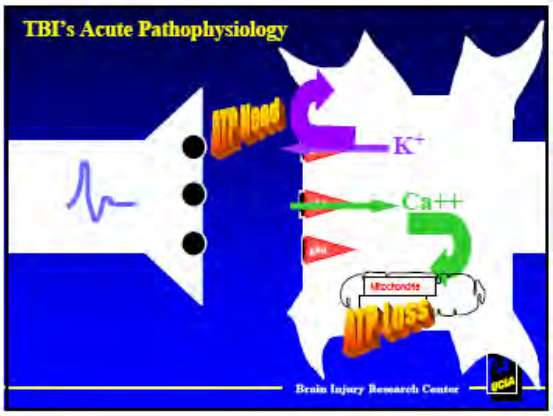

TBI's Acute Pathophysiology
K+
Na+
Ca++
Brain Injury Research Center
UCIA

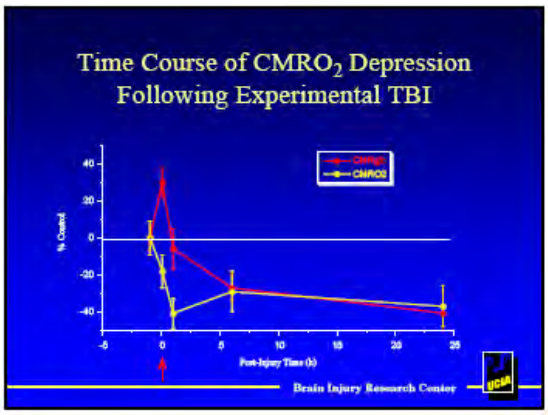

TBI's Acute Pathophysiology
ATP Need
K+
Ca++
Mitochondria
ATP Loss
Brain Injury Research Center
UCIA

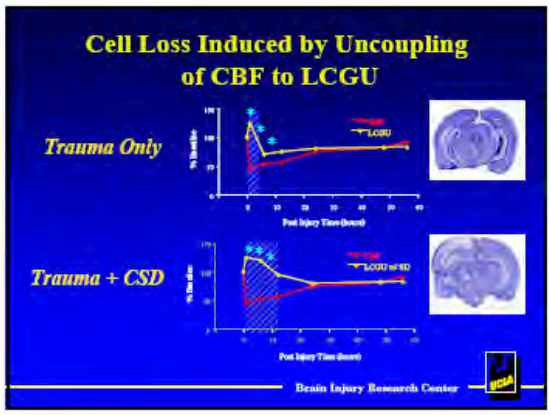

GLUCOSE
LACTATE
MCT
BBB
NEURON
ASTROCYTE
GLYCOGEN
G-6-P
Pentose Shunt
PYRUVATE
LACTATE
hexokinase
glucose-6-phosphatase
TCA
ACETYL-CoA
Brain Injury Research Center
UCIA

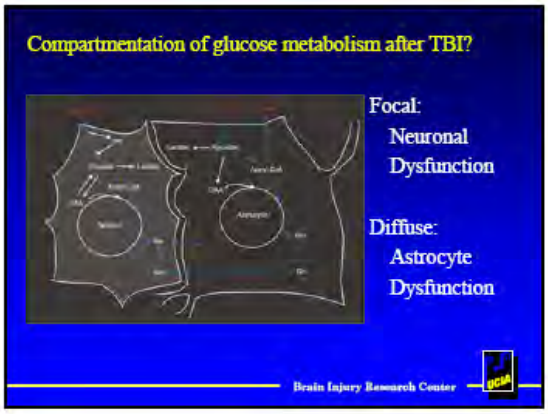

Acute Hyperglycolysis
NMDA receptor-mediated release of K+ resulting in an increase demand for glucose along with the production of lactate
2DG
Increase In Cerebral Lactate
Brain Injury Research Center
UCIA

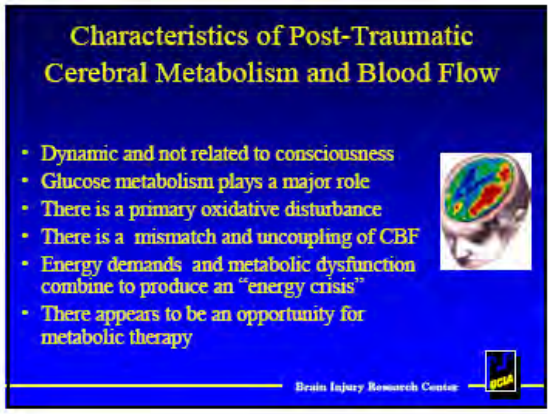

Hyperglycolysis is Followed by a Prolonged Period of Reduced Glucose Utilization
Mild, Moderate or Severe
Hyperglycolysis
Metabolic Depression
Hours Post-Injury
Days Post-Injury
Brain Injury Research Center
UCIA

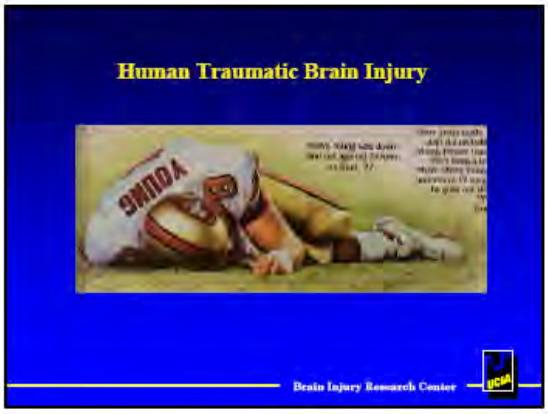

TBI's Acute Pathophysiology
ATP Need
K+
Ca++
Mitochondria
ATP Loss
Brain Injury Research Center
UCIA

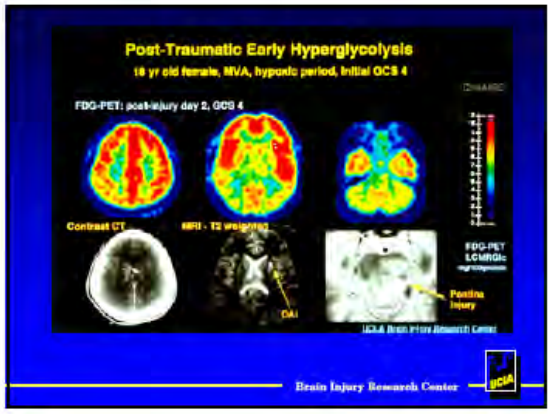

Time Course of $CMRO_2$ Depression Following Experimental TBI
Brain Injury Research Center

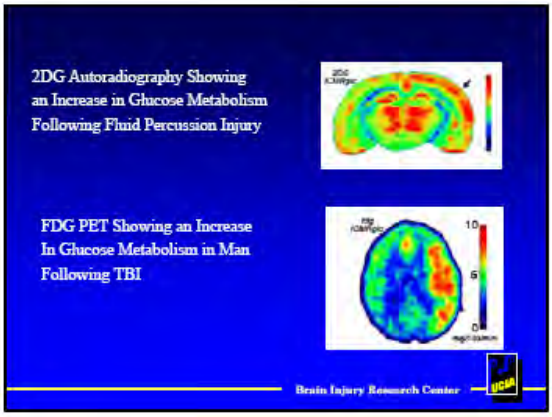

Cell Loss Induced by Uncoupling of CBF to LCGU
Trauma Only
Trauma + CSD
Brain Injury Research Center

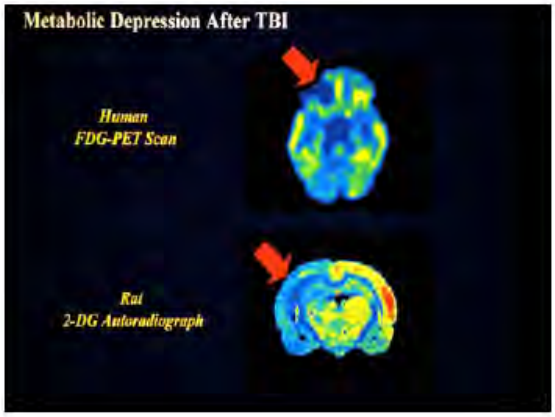

Compartmentation of glucose metabolism after TBI?
Focal:
Neuronal Dysfunction
Diffuse:
Astrocyte Dysfunction
Brain Injury Research Center

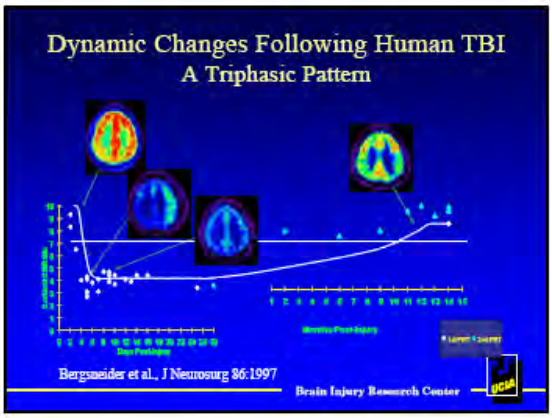

Characteristics of Post-Traumatic Cerebral Metabolism and Blood Flow
Dynamic and not related to consciousness
Glucose metabolism plays a major role
There is a primary oxidative disturbance
There is a mismatch and uncoupling of CBF
Energy demands and metabolic dysfunction combine to produce an "energy crisis"
There appears to be an opportunity for metabolic therapy
Brain Injury Research Center

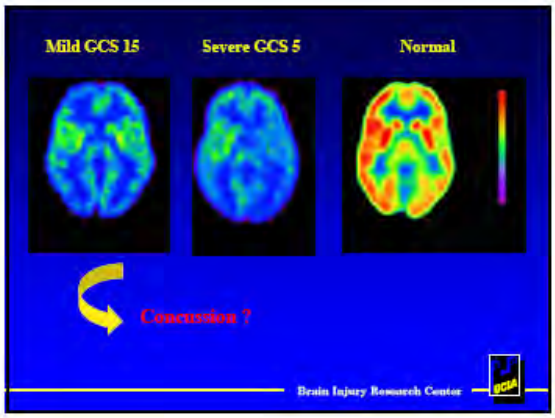

Human Traumatic Brain Injury
Brain Injury Research Center

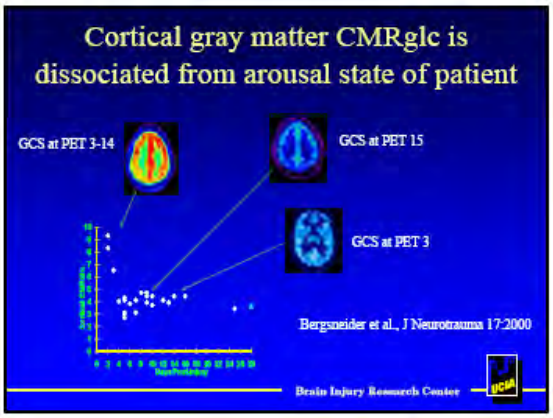

Post-Traumatic Early Hyperglycolysis
FDG-PET: post-injury day 2, GCS 4
Contrast CT
Brain Injury Research Center

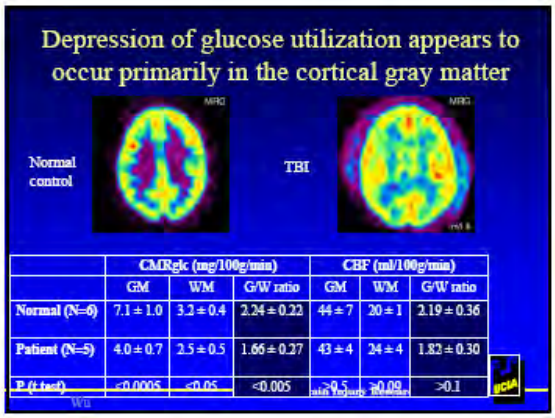




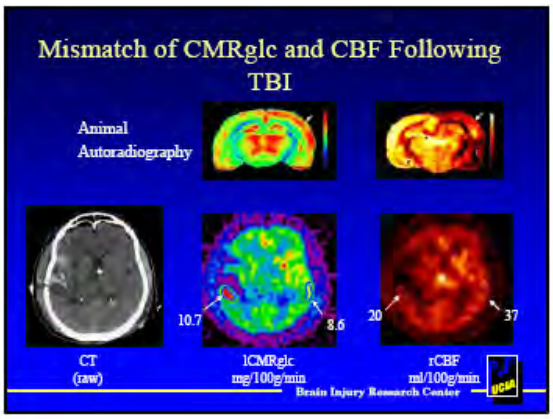


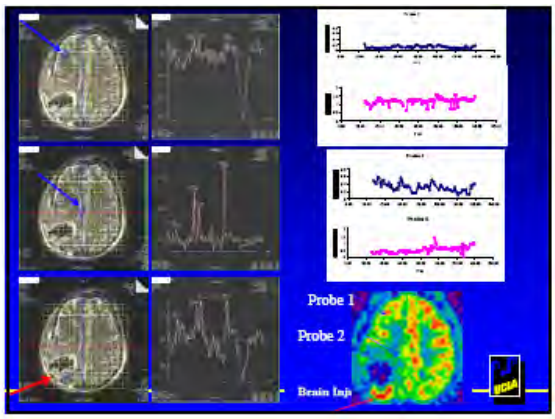


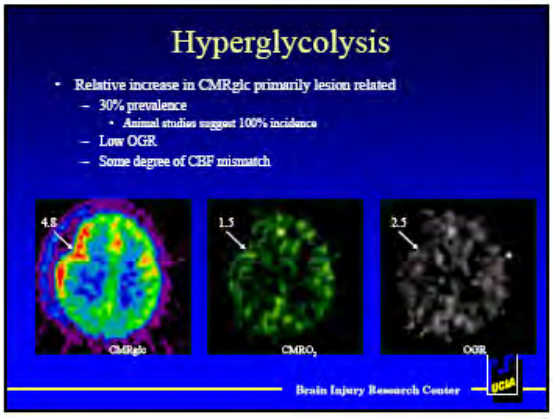


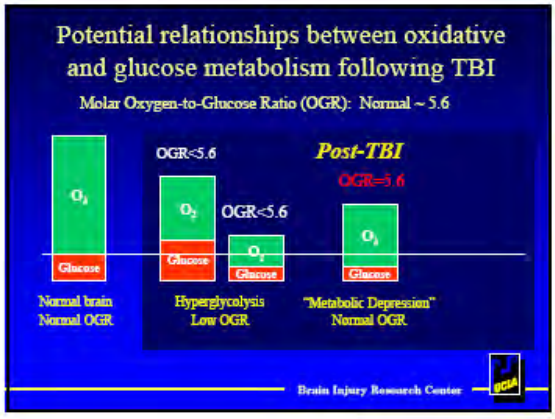


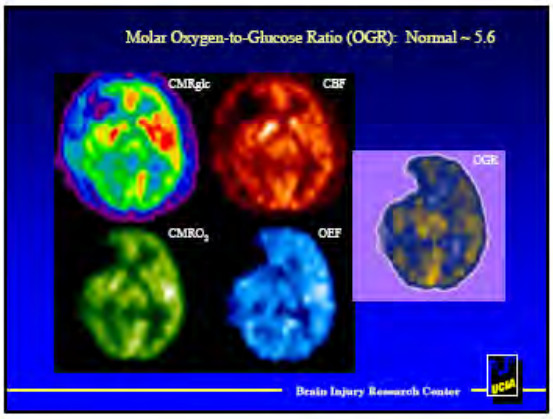
	CMRglc (mg/100g/min)			CBF (ml/100g/min)		
	GM	WM	G/W ratio	GM	WM	G/W ratio
Normal (N=6)	7.1 ± 1.0	3.2 ± 0.4	2.24 ± 0.22	44 ± 7	20 ± 1	2.19 ± 0.36
Patient (N=5)	4.0 ± 0.7	2.5 ± 0.5	1.66 ± 0.27	43 ± 4	24 ± 4	1.82 ± 0.30
P (t-test)	<0.0005	<0.05	<0.005	>0.5	>0.09	>0.1

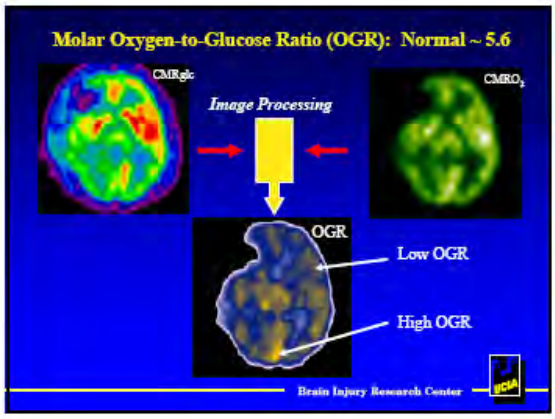

Mismatch of CMRglc and CBF Following TBI
Animal Autoradiography
10.7
8.6
20
37
CT (raw)
lCMRglc mg/100g/min
rCBF ml/100g/min
Brain Injury Research Center

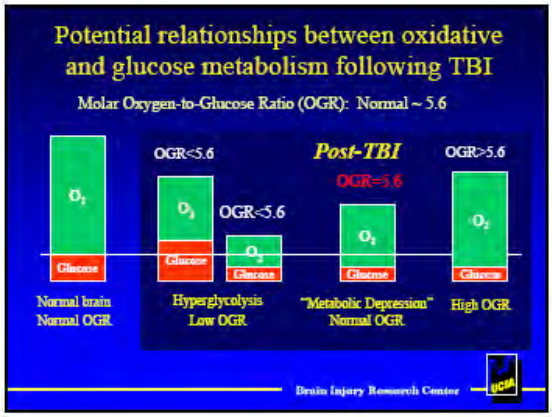

Probe 1
Probe 2

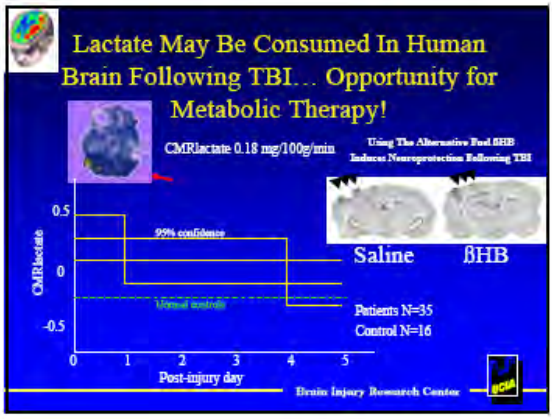

Hyperglycolysis
Relative increase in CMRglc primarily lesion related
30% prevalence
Animal studies suggest 100% incidence
Low OGR
Some degree of CBF mismatch
4.8
1.5
2.5
CMRglc
Brain Injury Research Center

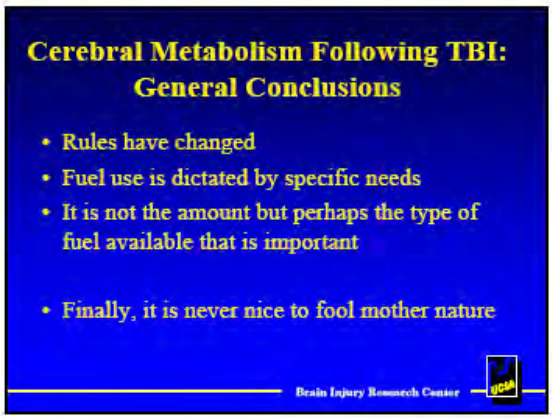

Potential relationships between oxidative and glucose metabolism following TBI
Molar Oxygen-to-Glucose Ratio (OGR): Normal ~ 5.6
OGR<5.6
Post-TBI
OGR=5.6
OGR<5.6
Glucose
Normal brain Normal OGR
Hyperglycolysis Low OGR
"Metabolic Depression" Normal OGR
Brain Injury Research Center


Molar Oxygen-to-Glucose Ratio (OGR): Normal ~ 5.6
CMRglc
CBF
OGR
OEF
Brain Injury Research Center


Molar Oxygen-to-Glucose Ratio (OGR): Normal ~ 5.6
CMRglc
Image Processing
OGR
Low OGR
High OGR
Brain Injury Research Center

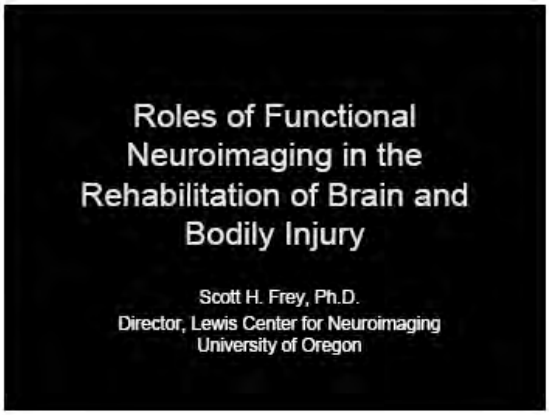

Potential relationships between oxidative and glucose metabolism following TBI
Molar Oxygen-to-Glucose Ratio (OGR): Normal ~ 5.6
OGR<5.6
Post-TBI
OGR>5.6
OGR=5.6
OGR<5.6
Glucose
Normal brain
Normal OGR
Hyperglycolysis
Low OGR
"Metabolic Depression"
Normal OGR
High OGR
Brain Injury Research Center
UCIA

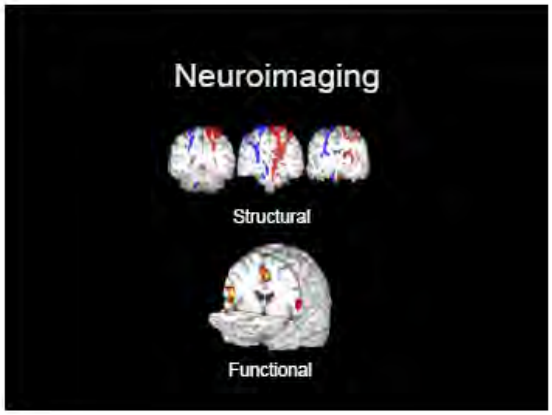

Lactate May Be Consumed In Human Brain Following TBI… Opportunity for Metabolic Therapy!
CMRlactate 0.18 mg/100g/min
Using The Alternative Fuel BHB Induces Neuroprotection Following TBI
Saline
βHB
CMRlactate
95% confidence
Normal controls
Patients N=35
Control N=16
Post-injury day
Brain Injury Research Center
UCIA

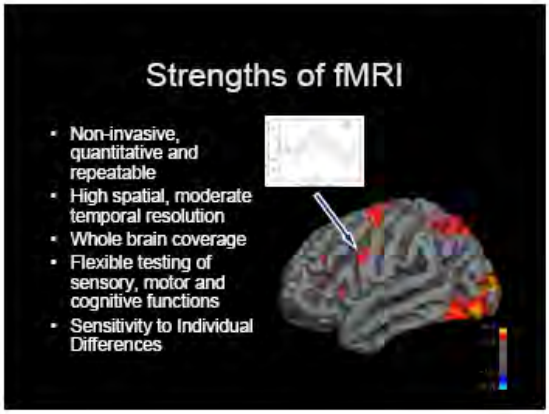

Cerebral Metabolism Following TBI: General Conclusions
• Rules have changed
• Fuel use is dictated by specific needs
• It is not the amount but perhaps the type of fuel available that is important
• Finally, it is never nice to fool mother nature
Brain Injury Research Center
UCIA

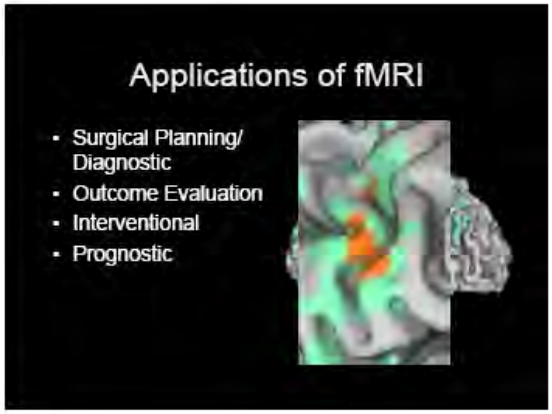

Brain Injury Research Center
UCIA

Use of fMRI to Assess Brain Function During Rehabilitation
Scott Frey, Ph.D.
Director of the Lewis Center for Neuroimaging, University of Oregon



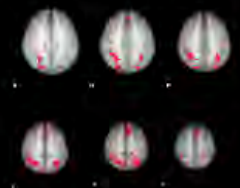






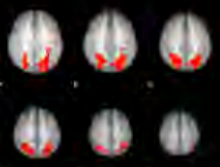
Neurally-Inspired Therapeutic Interventions

- "Right" unilateral amputees (N = 12)
- Increased activity in response to observation of "bilateral" vs. unilateral hand stimulation

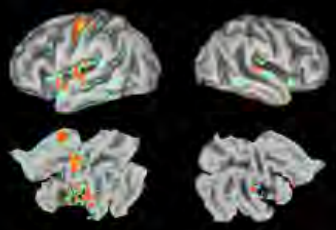


Neurally-Motivated Therapeutic Interventions

- "Right" unilateral amputees (N = 12)
- Increased activity in response to observation of "bilateral" vs. unilateral hand movement

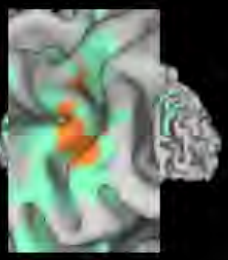


Predicting Functional Recovery



The Future

- Optimization & Individualization of Rehabilitation Protocols
- Improved Integration of Assistive & Prosthetic Technologies



Thank You

Frey Lab Support from:

- TATRC
- ARO/ARL
- NIH/NINDS

Appendix B
Transcript of Discussion

AMERICAN INSTITUTE FOR MEDICAL AND BIOLOGICAL ENGINEERING
1901 Pennsylvania Avenue, N.W., Suite 401
Washington, D.C. 20006
(202) 496-9660

AIMBE-Military Collaboration:

BIOENGINEERING CHALLENGES OF BRAIN TRAUMA

8:00 a.m. to 4:00 p.m.
Wednesday, February 20, 2008

National Academy of Sciences Lecture Room
21st and C Streets, N.W.
Washington, D.C.

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P R O C E E D I N G S

Introduction and Welcome

DR. GRUNDFEST: It is my pleasure to welcome everybody to this joint TATRC-AIMBE day on neurotrauma imaging and rehabilitation.

You might wonder how we came up with this particular format and how it evolved, which requires a little explanation because it is not your usual meeting.

AIMBE, the American Institute for Medical and Biological Engineering, has a focus on policy, on bringing engineering expertise to government and industry, and serving the needs of the biomedical engineering community in its broadest sense. TATRC, which is the Telemedicine and Advanced Technology Research Center of the Army, focuses on state-of-the-art and leading-edge technology development for the Army.

Since I have been involved with both organizations, I thought there might be an opportunity to bring the two together on a specific focus topic, and in talking with my co-host, Ken Curley the chief scientist at TATRC, and with people at AIMBE, we felt that this might be a good first step to bring people together to sort of build bridges between the engineering community and the Army and the larger DoD as a whole.

This serves the missions of both. AIMBE is an organization dedicated to bringing expertise in medical and biological engineering to government. It also has a role in supporting research in these areas and supporting educational activities, and at the same time, TATRC, which you will hear more about from Ken Curley, has a broad portfolio of biomedical research that really covers the gamut from telemedicine to brain trauma to recombinant DNA.

Given these large areas of potential overlap in the direction, I thought it would be very valuable to try and bring people together. So this is an experiment. This is an effort to see if the format works, to see at the end of the day there can be some information exchanged and perhaps some collaborations built, and if nothing else, let the Army know where some of the state-of-the-art is in the engineering side that is outside the DoD, and from the other side, let the engineers know what the needs of the Army are, so they can work on those problems.

This is very much a free-flowing meeting. We want to keep it open. We want to discuss ideas, and we want very much for people to express what they think are the pros and cons of various ideas and allow for discussion. So, in fact, you will see in the program, there are discussion panels, and they are meant to stimulate interaction with the audience.

I think that if this format works, we will hopefully see this on other topics, and hopefully, this will also evolve into a more formal or larger program between the Army and AIMBE and perhaps others within the Federal Government.

With that, I would like to introduce my co-chair, Ken Curley. Ken is the chief scientist at TATRC and has a long strong interest in neurosciences and neurology and neurosurgery and was absolutely critical in putting this together, and I want to thank him and all the people at TATRC.

I also need to thank Jennifer Ayers, the Executive Director of AIMBE, and Jason Rivkin who is, unfortunately for us, leaving AIMBE and going to work in the Pentagon. So maybe we can have some more collaborations through that line for helping put this meeting together.

Ken?

DR. CURLEY: Thank you, Warren.

Thank you, everyone, for attending. I want to also thank the AIMBE in particular for inviting us to be involved, and I would like to especially thank all the speakers and panelists who are going to be with us today. I think you can tell by looking at the agenda that it is really an excellent group, broadly representative of the things that we are interested in at TATRC.

Just a little housekeeping, each speaker is going to have 15 minutes, and I am going to be waving like an idiot down here in my chair. I have also got my cane to yank people off the stage, but it would really help if we keep to that. I know it is hard. Our speakers are all so deeply entrenched into the work that they are doing and so excited about it that each one could easily do a couple hours on their work for us.

Normally, this kind of meeting, I might do in a 2- or 3-day format, so we could do that, but unfortunately today, we don't have that luxury, and the other issue being is that for those of yo who are staying locally, there is a weather advisory. So any later we get out of here beyond 3:30 or 4:00, we are going to be looking at some really interesting commuting conditions. Last week, it took about 4 hours to get to Northern Virginia from here. So let's try to keep the timing in mind.

The way this is going to work is there's going to be three different sessions, the first on imaging, the second on monitoring, and the third on therapeutics. There will be a number of speakers, and then there will be a panel.

The panel are distinguished experts familiar with the area that is being spoken about. Each panelist will have 5 minutes. In some cases, they are going to share some of the things they are doing, but they are also going to expand on what they have heard today. When each panelist is through, then we are going to open it up to the audience. That is where I hope sort of the meat, the beef of this meeting will come from is getting some feedback from the audience about areas that you think would be important for us to look at.

As Warren said, I am the Chief Scientist at the Telemedicine and Advanced Technology Research Center. I am an IPA with the Henry M. Jackson Foundation for Advancement of Military Medicine. I am also on the faculty of Uniformed Services University of the Health Sciences, and my background is in clinical and basic neuroscience.

For all the speakers, this is your control and sort of a laser pointer. So, if you need to use a laser pointer, I will put this up here. This is the yellow button, and that is a little better.

TATRC's mission. Basically, we manage congressional special interest research. As our name suggests, we basically manage nothing but telemedicine and advanced technology research early on, about 12, 14 years ago when TATRC began. We expanded into teleradiology, medical informatics, hospital information systems, for example, and around 2000, we started expanding into other areas like medical modeling and simulation, and we have continued to grow, and over the past couple of years, we have grown exponentially.

Our vision is to be the model of government enablement of technology transfer to use, and in simpler terms, that just means we want to get things into the soldiers' hands, so the medics can take care of soldiers and so that the nurses and physicians can take care of their patients.

This is just an example of TATRC's research portfolio and how broad it is. There's black lines around these boxes, but that is not necessarily how it works. We have projects that cross two or three of these areas. So each of these portfolios has a portfolio

manager, and I am the portfolio manager for neuroscience, and my associate, Dr. Cardin who is hiding in the back is my deputy. Basically, we have two folks like that for every portfolio.

Again, this actually changes and grows on almost a continual basis, and as you can see, we have everything from medical robotics over to nanomedicine and biomaterials. The areas that have really been hopping in the past couple years have been neuroscience and regenerative medicine, unfortunately, as a result of the current conflicts.

This is just an example of TATRC's strategic partnerships. We are part of the U.S. Army Medical Research and Materiel Command, and so we work closely with the research area directorates within that command. We also are establishing some relationships with the Naval Health Research Center and with the United States Air Force as well. We also work closely with a number of Army, Navy, and now Air Force medical centers, and you can see our extramural partners. That is just a partial list. The full list would be in that size type all the way across the slide. So we have quite a number of partners we work with.

The history of this portfolio dates back only about 2 years. When I came to TATRC, I was doing surgical navigation and medical modeling and simulation. I didn't get to do neuroscience until about 2 years ago. Unfortunately, again, with the incidence of polytrauma, including amputations, traumatic brain injury and spinal cord injury, there came a number of congressional special interest programs related to addressing those issues.

One of those, the larger one that you might be well aware of, is the congressionally directed Medical Research Program which is another organization within the Medical Research Command, and they have just completed a period of proposal review for about $300 million of research money for the civilian sector for looking at TBI and PTSD.

As I already noted, neuroscience crosses many of the other TATRC portfolios, and we have utilized funding for neuroprosthesis, specifically vision. Actually, Dick Norman is here. He is the principal investigator on that with Bradley Greger. Diagnostic imaging, diffusion tensor imaging, we are doing at USC, and I just want to show you sort of a graphic of how our portfolios work.

These lobes are basically what we call subportfolios. So, within neuroscience, we have traumatic brain injury, PTSD, and other behavioral pathologies of war, imaging, spinal cord injury, human performance and rehabilitation, neurodegenerative diseases, primarily Parkinson's and ALS and Alzheimer's, and neuroprosthetics. Around the outside, we have areas that are starting to grow, pain management, ocular and hearing issues, telemedicine applications. We are actually doing some telementoring with Landstuhl Regional Medical Center using a telemedical robot.

Also, research on education and training components, we have a program that we are working on through the Small Business Innovative Research funding where we are developing a training system that uses virtual reality to train providers how to do nerve blocks out in the field, so that they can actually provide regional anesthesia for patients in the field, as well as all the way back into the medical centers. The patients are much more comfortable that way, and they don't have to be sedated with a narcotic analgesia, and that has been quite successful.

Specifically, today, we are talking about neurotrauma and TBI. As far as what we are managing at TATRC, we are looking at biomarkers for acute and chronic TBI, and that is blood and CSF-based biomarkers, as well as imaging-based biomarkers. We are looking at therapies directed at those biomarkers. We are also looking at the development of a neurotrauma database, regenerative medicine issues, and therapies for post blast vasospasm. Actually, you will hear about some of these things today from other speakers.

So, with that, I thank you for coming, and I invite Colonel Geoff Ling up to give sort of an overview of neurologic care in the military.

COL LING: Good morning, everybody. Thank you very much for allowing me to spend this day with you. I would like to thank all of you who are participating. It is great to have civilians as august as this group is to help us try to solve some of the problems that we have in our very unique community. In the end, I think that it is going to have tremendous impact on the delivery of care to civilians as well. So this is one of those kind of unfortunate opportunities that arise from something as like war.

So what we are going to do today, I was asked by Ken to give you, very briefly, about 10 minutes on where neurocare stands currently in the military.

The picture that you see up here is the entrance to the 452nd Combat Support Hospital which was during my first deployment in Afghanistan. A lot of you who are familiar with hospitals, that is not what most hospitals look like when you got to get to the front door, but that is what it looks like over there.

What is the mission? Let's really define our space, as it were. The mission of the military medical services is just this, it is to preserve the fighting force. That is, in fact, the Army's medical regimental motto.

What does that mean? Well, fundamentally, it means exactly what it says. Our job is to try to take care of soldiers and turn them around to go back to the fight. That is very different than in the civilian sector where you take somebody off the playing field or you take somebody out of work that have a good period of rest and recuperation, which they should have, but those that can be returned to the fight, you return them to the fight. So what it means is, very simply, you apply the medical resources that best support the front line. It is very simple. We have a limited number of soldiers. They have a lot of work to do. We have got to get them back into the fight.

Those that cannot go back to the fight, you don't use those limited resources other than to try to save their life and get them the heck out of there. It is as simple as that, and when they go back, then we are going to give them to Walter Reed, Germany, Brook, these other places. We will give them the standard of care that you will get in any hospital that you can find, whether it is Fairfax Hospital, G.W., Georgetown, or wherever, and the NIH is a wonderful partner in that.

When you take care of people stateside, we are going to give them stateside care. There is nothing magical or special about medical care at that point, and we are very proud of the care that we give. The JCAHO review of Walter Reed recently was over 96 percent. That is the highest of any hospital in the city. So we do give a high standard of care to the standards of JCAHO, to the standards of the NIH, so on and so forth, but this is not our lane anymore, quite frankly. This belongs in the world of civilian medicine, and we will do the best we can.

Our world is here. This is Echelon 1 through 3, and this is my opinion, and I think that it is shared by Dr. Vandre who is here and Ken as well. This is where a lot of our efforts need to be in terms of research, in terms of the effort for our portfolios and so on and so forth. This is the area that the NIH with its $30-billion budget -- by the way, it makes them the twentieth wealthiest nation in the world, but with their $30 billion budget, they are not interested in this, and I understand that. That is not part of the public health. This is our world.

Echelon 1 is your medic. Echelon 2 is a forward surgical team, and it may or may not exist in many places. When I was in Iraq, for example, it did not exist in Baghdad.

They didn't need it. So you went from Echelon 1 directly to the combat support hospital, and Echelon 3, which is the combat support hospital, is the highest level of care typically that you are going to find in Iraq and in Afghanistan today.

In World War II, that wasn't true. In World War II, they had theater-fixed facilities. They had that in Vietnam as well, such as in Saigon, which looked like a mini Walter Reed essentially in theater. We do not have that in Iraq or Afghanistan. What we have are combat support hospitals. So the flow begins here with these fine individuals providing care up front.

There is the paradoxical length of stay, and the paradoxical length of stay is that the pre hospital tends to be longer than in the civilian sector. In the civilian sector, you get in a wreck on the roadside, you call 9/11, they fly in, they scoop you up, and they get you out of there within 10 or 15 minutes. In Iraq, it is actually pretty fast. You usually can get a bird in, in about 10 or 15 minutes and get them to the cache in about that amount of time, and in Afghanistan, it is very long. When I was over there, it took sometimes up to 13 hours to get somebody to the cache, just because of the mountains. It is very dangerous over there, so on and so forth, very hard to fly in those kind of conditions. In Desert Storm, it was 4-1/2 hours, to give you an idea.

I would point out that this is today's war. I don't know what tomorrow's war will be like, but today's war, we have complete air superiority. If that changed, that would, of course, prolong this.

However, once you get to the hospital, time is really short. The idea is to get them stabilized and get them out.

This is a CCAT team that I came back with, really just amazing individuals. They have not lost a single patient in the 6 years since 9/11. So, really, phenomenal care is provided. We at the cache will take care of the patients, stabilize them as best we can, and then the Air Force takes over and gets them out of the war zone as fast as possible. So it is a paradoxical length of stay, longer pre hospital, much shorter at the hospital.

The combat medic, a lot of people think is like your paramedic EMT that are firefighters. They are not. To get to be a paramedic, as you know, it takes 54 weeks of dedicated training to be on your local typical fire departments, 54 weeks of training that is around the clock, and then regular yearly updates. Combat medic is 24 weeks of basic medical training, 24 weeks, and that is after basic infantry training, which is 10 weeks long. They get 24 weeks of learning how to be a medic, and then they are out in the field.

There is usually one medic per platoon, generally. You can increase that number if you think you are going to be in a big firefight and so on and so forth, but typically, there is one per platoon.

They are assisted by what we call "combat life savers." This is basically a rifleman who is given a couple of IVs and taught how to start an IV and maybe some bandages. It is a 2-week basic aid course. It just gives you extra hands is what it does.

The other thing that is amazing that you should know is they have an extraordinarily high casualty rate. In wars past, they have the second highest casualty rate of any military occupational specialty, second only to snipers.

ATTENDEE: [Inaudible.]

COL LING: That is right. It is a very high casualty rate.

I don't know, Colonel Vandre, if they are the second highest in OIF/OEF, but they were in Vietnam.

ATTENDEE: [Inaudible.]

COL LING: There you go, so a very high casualty rate. In this war, it wouldn't be surprising because, as you know, our adversaries like the idea of setting up what we call secondary and tertiary to ID blast. In other words, they wait until the medical people come, and then they set off the second blast. It has been a modus operandi that they have had. So these are very high casualty rates.

These people are very dedicated. They are really, really very dedicated, but they don't have the level of training that your typical firefighter EMT does, just to let you know that.

And the other thing too is that they typically have to carry what they need on their back. So they typically carry a 21-pound A bag, and that is on top of a 75-pound patrol pack.

You guys have all gone camping. How many of you have carried 90 pounds on your back when you go camping, and by the way, nothing hanging off the front of you? Because in case something starts shooting at you, you got to be able to dig a hole and get yourself into it as fast as possible. So all 90 pounds is on your back. Nothing hangs off the front like all these fancy packs are, and if you are a Special Forces medic, you are carrying 125 pounds because those guys go off for longer.

So, when you tell them, "Oh, I have got this little widget I want to throw in your pack," they are not too excited about it because they are already sawing off the handles off their toothbrushes to gain some weight. So anything that you want to put in, you have to take something out. You just have to understand that is just the way they think.

Forward surgical teams, I could spend a lot of time on this thing, but generally, that is the aid station of today. That is what the aid station of today is.

A couple of these do exist out in Afghanistan. None to my knowledge exist right now in Iraq.

At the cache, it is an interesting place, I will tell you. In Afghanistan when I was there, there were 15 doctors at the cache, and when I was in Iraq, there were 30 doctors in the cache. That 30 doctors includes the pathologist, includes the dermatologist, and it includes the psychiatrist -- and the psychiatrist, by the way, is a very busy guy -- and the radiologist. So, when you take those guys out of the loop, in other words, the people who don't provide emergency care, the case load becomes extraordinary.

In Afghanistan, we would get four traumas a day and 25 non-traumas, and those are mostly humanitarian. Over 90 percent of the cases actually were Afghanis, and they were land mines, accidents, gunshots, and all that. That number has gone up towards the war side recently because of the increase in IUDs, but that was my experience when I was there.

Baghdad was different. That was a hardcore war. We were getting 60 traumas a day. Remember there are 30 doctors, 25 of which are being able to provide emergency care. So 60 traumas a day, 100 non-traumas, still 85 percent were Iraqis. So the vast majority were still Iraqis, but nevertheless, a heavy, heavy war thing.

Those of you who have worked in emergency rooms and all that, think about how many level one traumas come into your hospital a day and how many doctors you have and nurses you have there. Well, flip that. We have 60 a day. Sixty a day would be considered mass casualties in any hospital in the District of Columbia, I can promise you that. That was a typical day. That was just going to work.

So, in that kind of environment, you just do what you can, and that is where a lot of the research that we are talking about today is going to be applied, in that environment.

The clinical practice, I will tell you is not meatball surgery like they would show on "M.A.S.H." You practice the highest level, ethical, moral practice. You always give standard of care when you can give it, always, always, always, and we use all the validated algorithms that all of you are familiar with, ACLS, ATLS, Brain Trauma Foundation guidelines. So a lot of the things, like the non-invasive ICP monitor, we need this because it is part of the Brain Trauma Foundation guidelines, and for us to give that, we need it.

This is a great place to work, I must tell you. The "jerk off"-ness is very low there because, when you go to the hospital, there is a lot of jerk-offs in the hospital, the guys who are the super specialty surgeons or something like that. Well, I will tell you what, that goes away when you are out there, and that is what is kind of neat. Even the most highfalutin neurosurgeon or cardiosurgeon, they are just a regular cutter when you get out there. They find themselves up to their elbows in it, and their arrogance goes away in a big hurry because, if you think that you can be alone, get out there and do this for a while, and you will find out what loneliness is all about.

This is a classic picture of getting a patient ready. This is a casualty that came in, and you can see Eklin [ph] is already cracking the skull while we are still starting lines and just haven't got him intubated, but you just have to have that pace as it goes. So it is a good thing.

In the TBI of modern war -- and that is really what ita comes down to -- it has gotten to be, as you know, much more prominent in the media and much more prominent in all of our psyches. Historically, it has always been there. It has always been there. About 15 or 20 percent of all battle-related casualties usually involve the head or the neck, and 50 percent of the patients who die of wounds, that is, after they reach medical care, die because of neurological injury.

So, because of that, it always has been there, but there was a certain neolism about it, and that neolism probably was built upon what we were able to do in the civilian practice. Even today, we don't have a neuro-rescue drug. It just doesn't exist. There's a lot of promising things, that is true, but it just doesn't exist. So, in clinical practice, we have no neuro-rescue drug.

The most useful thing we have in clinical practice are the Brain Trauma Foundation guidelines. They have been very helpful, but because of that, there happened to be a certain neolistic view that there is nothing you can do for brain injury, so, therefore, don't do anything, and that is kind of a self-defeating attitude. Really, it is because my argument would be if you don't do anything about pneumonia, you are going to die of pneumonia.

I am glad, especially among all the people in here, that that neolistic approach has now been sort of abandoned, if I may, but for a long time, especially the beginning of the war, that was the thought, that if you had a head injury, you are going to die, so don't do anything about it.

The question I think at hand right now is how much of it is out there, how much brain injury is out there. Nobody really knows. Nobody really knows. Among the moderate to severe head injuries, which are very easily definable levels of injury, at the height of the war, we were probably getting 30 or 40 cases a month, a couple a day. Now that the war has wound down tremendously, as you know -- we are down to about a third of the casualty rate that we were last year -- that number has precipitously dropped as well.

These are good things. We want fewer casualties, but at the height of the war, that is how much we are getting.

You have been hearing about a lot of patients who have this mild TBI, and that is a concern. I think all of us in this room have that concern. It is driving some of the research that we want being done, but we don't know what the number is. Huge numbers have been reported, 40 percent of the deployed soldiers have suffered a closed-head injury at some point in the war. That means between Colonel Vandre and me, one of us have got a head injury. So I am not exactly sure which one it is. Maybe both of us, but the point is that that is a very high number, and that includes the cooks and the bookkeepers and everybody else. So it really seems to be almost an unrealistic number, but the fact of the matter is it is probably a high number.

The question is really how many is that. We truly don't know, and I know the DVHIP are trying hard to get that data. We just don't know.

Secondly, how many have suffered more than one injury? It is a very dangerous business, soldiering in a war, and that is a very relevant question. So we don't know that.

This is the really key issue. How many have persistent symptoms that are lasting 6 months to a year out? The so-called delayed brain injury or delayed PTSD or whatever you want to call it, nobody really knows that either. Nobody really knows what it is, quite frankly. You know there is an active debate right now in the medical literature, even in the New England Journal, that is deciding whether or not it is all PTSD, some of it MTBI, maybe a combination of the two, who knows, but we need to find that out.

So, at the end of the day, what are the gaps in the world, in the land that we live in? I would say the gaps, they are broad. These are broad topics because we could pick out from within it, but certainly, in my guise as a DARPA program manager, these are the things that I zero in on, and I know my friends, Ken Curley does and Frank Tortella and Colonel Vandre and the rest of us that are in this room right now do.

One of them is the epidemiology. You got to know how much of a disease is out there. So I think this is an area that really needs a lot of focus, and we are getting some of that data.

The Joint Trauma Registry is helpful, and the Navy-Marine Casualty Database is helpful, but we really need a good strong epidemiology of the diseases. That is what we need.

Second is we need field-capable diagnostics. What is field-capable diagnostics? That is the non-invasive ICP monitor. That is the biomarker work that Ron Hayes and Dr. Hovda are doing, and that is looking at some functional outcomes, perhaps EEG or anything else, and that is ideally something like regional cerebral blood flow, things that we can use to help us manage our patients in the field. That is what we want. It is very simple.

Imaging. We would like something that is deployable and ideally something simple that doesn't require a radiologist. Waiting for a radiologist is very valuable, but honestly, way out in the field like that, it is improbable, especially with the demands on the bandwidth that is going on right now. If an operational commander had to send back x-rays on the limited bandwidth they have or fly a UAV, guess what he is going to do? So, if we can have simple deployable devices that could be point of care, great.

This is not to say that we don't have value for things like FMRI, diffusion weighted imaging, SPECT, and all that. We do, but as they get further back, it is going to

help us with our diagnostics. Quite frankly, right now what we need up front is to take care of these guys that are getting banged up.

The final thing is therapy. We all want a neuro-rescue medication. I know that Frank Tortella has a very promising drug that is entering clinical trial. I hope it works. I think we all hope it works, but a lot of us have been there and done that. We hope it works. With somebody like Frank wanting it, it stands its best possible chance, in my opinion, but we won't know until it is done. Even Frank, a good scientists, would admit that, also. We just don't know. We can save a rat. We can save lots of rats, but we can't seem to save our soldiers too well right now. So I hope this works, but we need one.

Having said that, there are other areas of therapy that we can leverage against, rehab, neurosurgery such as the post blast vasospasm that Ken is funding. That is very important work because these are soldiers now today that need this kind of therapy, and the rehab work that Paul Pasquina will talk about later today and Jack Tsao, these are really critical things.

Neurology critical care, we can make lots of inroads here while we wait for this to improve things.

Basic science, we can't get enough. At DARPA, as many of you know, I started a basic science program looking at explosive blast TBI. We need more of it. That can't be the only program. We need more of it.

Ideally, I would love to see us develop a preclinical model that doesn't use an animal. If we don't need animals, that would be the best. That would be my dream. My dream would be a predictive preclinical model that doesn't use an animal. That would be the best of the best. Maybe we will get one; maybe we won't.

So I end this with these pictures. These are my war pictures. This is a patient of mine. This is an Iraqi, a good guy, hit with an IED, and as you can see, he lost a good part of his face. That is brain, by the way, that is coming out of there. That is what is left of us eye. Literally, he took a bad hit. So the brain is extruding out the lower side of it.

This is him 8 hours later, after Jim Eklin operated on him. He did a frontal lobectomy, did a partial temporal lobectomy, turned a nice big flap, closed him up, took care of this guy for ten days. For ten days, I took care of this guy. He was very sick, as you can imagine given those kinds of injuries, but the end of ten days, he was following commands. He was awake. I could extubate him, and I sent him off to a civilian hospital. So, in spite of the fact that he looked like this, he ended up looking like this. He opened that other eye, which was a good eye, and he showed a high level of recovery. Does this mean he was normal? No. It does not. This takes us to the limit of what we can do.

So I thank you all for being here today because if we want him to go from here, to go from here, and then to go from the point where he can sit up and talk to us which is idea and possibly, if he would want to, go back to duty as an Iraqi police officer doing wonderful things for his own country, then that would be the ideal thing.

So, to do this list, we can't do it alone, and I am very pleased that we have such august scientists and academics such as yourselves here to help us take a look at some of the problems that we have that I believe are unique to our community and our situation, but one day I believe will translate themselves to take care of the patients that live next door to you at home.

Thanks a lot.

[Applause.]

DR. GRUNDFEST: We always appreciate Colonel Ling's presentations. I am sort of like playing the piano here while I am talking to you.

Now I would like to introduce Commander Jack Tsao of the United States Navy who is hobbling his way up. He had a little bit of surgery. He is on the faculty of Uniformed Services University of the Health Sciences.

Program Session I

Imaging:

The Current State of Technology and Challenges

CDR TSAO: Good morning, everyone.

DR. CURLEY: Before we get started, instead of the panelists sitting up here who are having to break their necks, the panelists can just stay in the audience until the speakers are finished, and then the panelists will come up.

Go ahead, Jack.

CDR TSAO: Okay. I am here this morning to give you a quick overview on TBI, as well as to sort of set the stage for the first part of the gaps that Geoff has nicely introduced, which is the imaging gap.

So, again, I ned to put the disclaimer that I am speaking my opinions as Jack Tsao, rather than representing the Federal Government.

This is an example of a brain from one of the casualties from the war who suffered a closed-head injury, TBI. So TBI can manifest in several forms. So, obviously, it is sort of penetrating gunshot wounds. Things that enter the skull cavity can cause a lot of damage, but one of the other major issues that we are facing is what happens with closed-head injuries, so people get exposed to an explosion, vehicle flips over, they hit their head, something hits their head. Closed TBI is one of the areas which can be missed if you don't look carefully enough for it.

Again, this is sort of the classic view on how TBIs are divided, from blunt injuries to penetrating injuries. Motor vehicle crashes are the most common things in the civilian sector, and war time right now, it is the improvised explosive devices.

At least 1.4 million Americans are affected by TBI, and as you can see, there are 50,000 deaths a year. So this is a major problem.

TBI in the military. Military members are, of course, at increased risk for TBI due to the nature of their jobs, but also sort of even during peacetime. This is an example of the West Point Rugby Team. That is where some of the first concussion studies were done out of, and then obviously, combat-related.

Here are some of the statistics I was able to get from the Defense and Veterans Brain Injury Center. They looked through July of 2007 at their numbers, and these are primarily derived from the casualty figures from Walter Reed Army Medical Center. Of the cases that they had come through this medical center, which is one of our tertiary hospitals, 30 percent have TBI. Cumulatively through all their sites, they have four civilian and about six or seven military sites. They have seen about 2,700 patients, and so the estimate of 30 percent may be on the high side, in talking to some of these other centers, but still it is a significant number of patients that they have seen who have had problems.

Overall, at Walter Reed, they have treated 1,250 TBI patients just from Afghanistan and Iraq conflicts alone, and then there are other civilian VA centers that they are partnered with. I have seen about 700.

What is the primary mechanism injury? It has got to be blast, and those of you sitting up close can see the shockwave of the blast as it moves through.

Mechanism of injury thought to be several possibilities, diffuse axonal, coup-contra-coup -- obviously, with penetrating, you have foreign body -- and then the image that isn't there is could there be some other mechanism associated with blast exposure.

Here are a couple examples of what happens when you have injury. In a closed-head injury, you can have hemorrhage, or penetrating, you can see sort of the skull has been taken off, brain tissue is extruding mid-line shift, and what appears to be a hemorrhage or edema.

So pathology, what happens primary injury, you obviously have injuries to the skull itself. You can have bleeding within the brain, as well as damage to the axons, the connections between the nerve cells and the rest of the body.

Secondary injury, you can have obstruction leading to increased pressure inside the brain, as well as blood flow metabolic changes elsewhere in the body, all of which can adversely affect the prognosis in the patient.

Operational definition of mild TBI, we use several different criteria from various organizations who are dedicated to studying this disease problem. This is one of the most difficult things to treat because as Geoff has alluded to, there is an overlap between post traumatic stress disorder symptoms and mild traumatic brain injury symptoms. So there is a lot of debate as to what component is the most important and what may affect outcomes, but to define somebody as having a mild TBI, they must have two conditions present. One, they had to have had an injury, and two, they had to have an alteration of consciousness. It ranges from just being dazed to sort of loss of consciousness.

The problem is right now in the field, a lot of times what we get is the patient reports, saying, "Oh, I think I was out for a few minutes." If they don't roll in with somebody from their unit, that is all we have to go on. They are taken care of at the point of injury. They are put on the evacuation helicopter. They show up at the hospital by themselves. If nobody from the unit is there with them, what we have to go on is what they tell us.

So what are the symptoms? Well, headache, dizziness, nausea, vomiting. Those could also be migraines, but in the setting of TBI, you have to think that there is head injury.

You see these also. They also overlap with post traumatic stress. So that is why there is a lot of debate right now as to what is truly going on in the brain that is causing the patient to experience these symptoms, is it the TBI itself, post traumatic stress by itself, or a combination, then fatigue, sensitivity, noise, decreased concentration, memory problems, and then anxiety, depression, irritability, and mood swings. It is not surprising that our soldiers and marines have this, and if somebody is shooting at your trying to kill you, I would have this as well.

Right now, there is no universally accepted guideline of care for mild TBI. So that is one of the gaps in our clinical knowledge. The majority of neuroimaging studies, in some of the papers that have been published, it has been suggested that they are not going to find very many things initially.

So what are the issues facing the military right now? Well, obviously the PTSD and TBI overlap. What happens if you get one concussion, you seem to get better, you are back out in the field, and you get another one? Is the damage cumulative? Is there a period where they are more at risk where they need to actually be held out of the fight and watched, and if so, how long is that period? That is yet to be defined.

Is blast exposure causing brain injury different than what we think of as conventional means of traumatic brain injury? Then does the information that we are getting

from sports concussions actually translate into the battlefield setting? Like are the cognitive difficulties that somebody has after a sports concussion the same as they might have after a blast concussion, and then what sort of long-term sequelae are we going to see, and then care coordination and getting a seamless transition from battlefield injury back to tertiary medical center, back to rehabilitation?

In terms of the military health care system, this is a quick overview. People at the front have their medic with them. Then they usually get shipped back to the battalion aid station, if they are able to walk. Otherwise, they go to the field hospital, which can either be mobile or fixed. So, if the unit is moving through territory, they will have a mobile hospital set up behind the front lines as one example. The other example is in Iraq right now, we have fixed hospitals where casualties are evacuated, too.

From there, everybody goes out to launch to Germany, which is our regional medical center there. People are either evaluated there for a few days for TBI and held up to 2 weeks and then go back to Iraq if they clear cognitively, or they get sent back to the U.S. for further care. If they go back to the U.S., they either end up at a tertiary hospital like Walter Reed Army Medical Center or National Naval Medical Center or Brook Army Medical Center in Texas, or they go to one of the community hospitals which serves their base.

Imaging technology. Walter Reed and National Naval both here in D.C. have surgical planning labs. They have advanced 3D rendering image fusion and reconstruction capabilities.

This is Dr. Curley, who kindly sent me images of what he had done, and then this is an example of an open skull injury and how they have managed to reconstruct what the tissue looks like.

So what are our knowledge gaps? Well, obviously, imaging is the key thing at the front. So how do we get better images?

Our hospital in Balad in Iraq has a CT scanner. It doesn't have an MRI scanner, however. Also, if you have penetrating injuries to the brain, you always have to worry about what is metal, what is metallic, and what is going to cause problems. So is there a better way to image using CT? Maybe CT profusion. Is there a way to get a portable CT that actually will move into the field with somebody? Is there a better way to do like transcranial Dopplers, for example, to measure blood flow and blood flow velocity through the large vessels of the brain?

Near infrared spectroscopy, I have seen used in some cases of mild TBI. Are there any other methods? Our panelists will discuss additional methods.

MRI at most hospitals right now in the military is 1.5 Tesla. Is it better for us to try to get 3 Tesla magnets or even higher strength to get better resolution of images?

How do we image closed-head injury? What is the optimal method of doing it? What is the best timing? Those questions remain to be answered.

Should we get a baseline MRI on every recruit? That is a lot of time and effort.

How much changes? We have young men and women joining up when they are 18. We know that the brain is still developing at that time. So is getting a baseline actually going to be helpful? Those are some of the issues that we are debating now.

Finally, in terms of new technologies, what should we be looking at? There's one or two studies going on that we are going to look at diffusion tensor imaging. People are

going to try to look at the tracts of the axons within the brain. Is that actually going to be helpful? We will see.

SPECT scans have been done by one of the hospitals out in Colorado because they don't have functional imaging. Does SPECT give us enough information? Is that something that we should routinely do, or is there something else? Then what is the best way of doing functional imaging? Is it to have somebody just sort of sit there and you get a baseline functional scan to see what areas are activated, or is it better to test them while you are doing cognitive tasks to see how they are able to bring in or recruit other areas for brain functioning?

So, at this point, I would like to turn it over to the next speaker and open it up to questions. Thank you.

[Applause.]

DR. CURLEY: Thank you, Jack.

The next speaker is Dr. Kraus.

Diffusion Tensor Imaging in Traumatic Brain Injury

DR. KRAUS: Thank you very much for having me speak today. I was really looking forward to this. One of the biggest challenges for me was trying to figure out how to talk about diffusion tensor imaging in 15 minutes or less. So I will do the best I can.

What would help me is if I could just quickly ask how many members of the audience have some basic familiarity with the principles of MRI?

How many have had an MRI?

Okay. Off to a good start.

How many work with DTI?

Great. Thank you. That helps me.

First, what I want to do is talk a little bit about diffuse axonal injury because this is the reason we are so interested in diffusion tensor imaging. This is a method based on MRI, as most of you know, that allows us the very unique advantage in that we can look more at the microstructure of white matter. So structural MRI will certainly show you white and gray matter, will differentiate it, but within the white matter, it won't tell you much about it. So DTI is sort of taking a step further and allowing you to look at the integrity of the white matter tracts.

It is still essentially structural imaging. It is not really giving you functional information per se. So, in some ways, you could say it might be complementary to true functional imaging, but what it will tell you is more detail about the microstructure of the white matter.

We do know that although white and gray matter are both damaged in traumatic brain injury, white matter tends to be more commonly involved, and I think in the more milder injuries, it plays a significant role, and obviously, there are some cases where the only type of neuropathology may be to the white matter.

We know that diffuse axonal injury can occur without direct impact to the head. We do know it occurs in milder injuries. Our recent work has shown that loss of consciousness is not required for us to find evidence of chronic changes in white matter.

A person's subjective impression of recovery also does not always seem to correspond with us finding residual pathology in the white matter, which is sort of another interesting point.

We also know another thing that is important to remember about diffuse axonal injury is sometimes it is thought of as being simply due to mechanical forces in terms

of being directly sheering, but actually what happens is it is really a process and not an event, and when these forces are applied to the brain, there is an effect that occurs at a membrane level, and multiple mechanisms will kick in, so that injury can occur over hours to days, weeks, and you may not see the final result in some cases even out to a year. Some studies have suggested it is that long before you see the final results of any atrophy or changes that are going to occur. So it really is a process.

So, in terms of the role of MRI or DTI early on, that is another issue to discuss. Our work is focused more on looking at people in a chronic phase of TBI, where I think you are at the point where they are more stable, you are not expecting any further changes, and it gives you an idea of what you might see further out.

So what is important is in some cases, it may be the only significant neuropathology. It does seem to correlate with neurobehavioral deficits, and as was mentioned earlier, a significant area that we are interested in is that whole sort of dubious area of mild head injury, what is clinically relevant neuropathology, how do you define it.

So there has been a lot of studies in this area so far. In DTI, which is a little bit more of a recent advance that we have at our disposal now to study this phenomena, there have been several studies done. They haven't always agreed on the areas of abnormal white matter. I think in general, a number of them have found that even milder cases do show some evidence of white matter change.

Methodologies vary. Magnets vary, processing, post processing, the way the data is analyze. There's a lot of variables here. So we are really not at the point where we can take the studies out there and kind of combine them in a real meaningful way yet, but hopefully, we will get to the point where we have a more standardized methodology. That would be ultimately the goal clinically as well not only for research purposes is to develop a specific standardized methodology of imaging. It might not just include DTI, but perhaps a range of imaging modalities that would adequately quantify and qualify the neuropathology in traumatic brain injury in a way that is meaningful, to correlate it to neurobehavioral outcome because that is ultimately what we are interested in seeing and in understanding how the symptoms and deficits that result, how these relate to the neuropathology.

When you talk about the overlap between post-concussive symptoms and PTSD, this is the type of imaging that may come in very handy in terms of trying to differentiate to some degree how much of a patient's symptoms may be due to the primary injury as opposed to PTSD or possibly a combination of both, which I would assume would be not uncommon.

So, basically, DTI in a nutshell, it is a modification of diffusion-weighted imaging, which has been around for sometime and used clinically in stroke. It is a nice way of identifying edema. It is very useful, but DTI took that a step further. Basser and a number of people developed a way to look at the same data you can get with DWI, but they developed a tensor model of looking at this. So that what they could do is look at directionality, get more of a three-dimensional idea of the white matter as opposed to just understanding the diffusivity.

The bottom line here is that what we are really interested in is this idea of the diffusivity of water molecules, and simplistically speaking, we are assuming that if there is no restrictions, water will diffuse as a sphere. If you think about dropping ink into a glass of water and you watch this diffuse, that is isotropic diffusion. It is going to diffuse evenly as a sphere.

Now, obviously in a biologic system, in the nervous system, there is going to be a lot of obstacles to diffusion. So diffusion is going to be anisotropic or restricted to various degrees in different tissues, and that is the key here. That is what we used to try to look at the structure of white matter tracts, which represent organized fibers. So there are fibers in gray matter. There are fibers there, but they are not as organized. They are not as directional as they are in white matter.

So what we are taking advantage of is the fact that we know that water is going to be more restricted in white matter. It is going to tend to have maximum diffusion along the major direction of the axonal bundles and less so in other directions, and if we can identify that at a voxel level, we can determine directionality, as well as looking at the integrity of the white matter, and then you can also get into looking at connectivity.

You can do tractography which allows you to grow, if you will, models of white matter tracts from a seed voxel based on statistical methods that allow you to look at directionality within the voxel and actually get what has been shown to be a fairly good, although it is mathematical, but it comes out to be a fairly good representation of what we see neuroanatomically.

So, again, what we are mostly interested in here is the diffusivity of water, and that is what the MRI technology allows us to look at.

There is a number of values that you can get, and again, this is very abbreviated, and I apologize for that, but what is important here is that the information you can get from DTI, you get a number of measures. One of the measures that is very important and most of you are familiar with is fractional

One of the measures that is very important and most of you are familiar with is fractional anisotropy. There are other types of measurements you can drive from the data. Fractional anistrophy allows us to look at the integrity of the white matter tract. In general, the values go from zero to 1. In general, the higher the FA value, the more organized the tissue is, meaning it has got more restricted diffusion. What you might see is perhaps, say, a .4 might represent the FA within a white matter tract.

This can be used. This is a nice mathematic way to look at the integrity of white matter. Now, there are nice pictures that can be generated from DTI, but visual inspection isn't going to tell you about subtleties. That is the problem. If somebody has significant white matter damage, yes. If you look at the images that you can get from this, you can inspect them and see that there are some changes, since we are more interested in trying to detect subtleties because I think it is that mile brain injury spectrum that has been so illusive and difficult to pin down in terms of defining neuropathology in relationship to neurobehavioral outcome.

In this picture, it sort of gives you an idea of what you come up with. Again, it is a mathematically derived picture, but it really proximates neuroanatomy fairly well, and what it tells you is the intensity of the signal reflects the density of the white matter in that area. So that the major tracts, like the corpus callosum, as you can see, a very dense large tract, is going to look the most intense on the map that is coded, so that intensity does reflect the value of FA.

As an example of what you can do with DTI, I am going to talk about the recent paper we had published in Brain. Again, work needs to be done in this area, but at least this will show you an idea of how it can be used, particularly I think in the chronic phases of TBI when you are interested in trying to define neuropathology, relationship to longer term neurobehavioral sequelae.

Methods overview, just briefly, we had 37 traumatic brain injury subjects that we painstakingly tried to select. This is very hard, as you know. This is a very, quote/unquote, "dirty population" in terms of comorbidity, other injuries, that sort of thing, and previous head injuries. So it really takes quite a while.

We tried to get a pretty well-screened group of single closed-head injuries. All severities, we looked at. So we had 20 milds, and we had 17 moderate to severe injuries.

They were a minimum of 6 months out from the injury. The majority were a year or more. So we had established that this was a relatively chronic population. We had 18 healthy matched controls, and all of these subjects underwent diffusion tensor imaging, as well as neuropsychological testing, fairly standardized, and we took the scores and we created domain scores with those, so in the areas of executive function or higher level-type cognitive function, attention on memory.

Just a bit about the acquisition because earlier the question was raised about 1.5T and 3T. Obviously with magnets, bigger is better to an extent. With larger magnets, you do get better signal to noise, but sometimes that does come at a price. However, we feel that the 3T for our purposes is more sensitive and has provided us what we think is good data. So we are biased, but we have a 3T scanner, and we prefer doing our studies on that.

So it is a sequence based on single-shot EPI. I won't go into this in great detail. One of the things, though, about this is the diffusion directions. Again, for this, more tends to be better. It just helps increase the spatial accuracy of what you are going. We had 28 diffusion directions we used for the analysis.

We generated eigenvalues, eigenvectors in FA. The ones of those that are important, I will mention again. This is just an example to show you visually what our RO1 masks looked like. We did region of interest analyses, and what we did, which is actually not practical in a clinical setting, is hand-drawn individual subjects, the entire tract. We had a medical student helping us, bless his heart. So he spent quite a while doing this, but it is the most accurate way to do it. It is, however, very time consuming.

Let me get to the results quickly here. Essentially, what was important here is we did find that all 13 regions of interest showed abnormality in the moderate to severes. There were three areas that showed statistical difference in the milds. There were areas that showed trends, but that was impressive to us. What we also did is we did an index, white matter load. This like this have been done with data before. It is not necessarily novel, but in terms of getting a single number to represent how much white matter damage, if you will, or dysfunctional white matter there was.

What was important here was that the milds, as well as the moderate and severes, were significant different from the controls in terms of the numbers of areas that were involved. So, if you look at the milds, 5.9 areas for the moderate severes, 9 areas, and this correlated. This is the neurocyte testing. What is important here is that the white matter load correlated with the neuropsychological testing. The cognitive function correlated, and it all fell in a spectrum.

So the controls, the milds, and the moderates, they fell in a spectrum in terms of neuropsychological or cognitive function. The white matter damage fell in a spectrum, and it correlated with the white matter load.

Real briefly, because I know I have like 30 seconds left, another analysis we did, which really shows promise -- and one of the reviewers suggested we did this -- this is a way to mechanistically look at, okay, you have shown that you have abnormal white matter.

The FAA values are off. What is driving this? So we took three regions of interest, and we did an additional analysis of axial and radial diffusivity.

This is a way of trying to determine differentially how much may be driven more by axonal damage or lack of integrity versus myelin involvement. That is the thinking, that more work needs to be done here, but what was interesting is the moderate to severe subjects showed both myelin and axon involvement. Whereas, the mild, which obviously didn't have as severely impaired white matter anyway, seemed to selectively have axonal involvement and not significantly different myelin or radial diffusivity changes compared to controls.

So these were just some questions that I think this type of imaging should raise, the role of DTI in further studying traumatic brain injury. I think it will have a unique role in blast injury as well, and as I understand, those studies may be already underway.

I was asked to just briefly say it doesn't compete with functional imaging per se. It is really complementary, and I think the combination of the two would give you unique information, and it does have an advantage over other types of structural imaging. I just don't know how deployable and portable it is.

I will stop there.

[Applause.]

DR. CURLEY: Dr. Cohen, our next speaker, he is from UCLA. He will be talking about the use of portable field SQUID devices.

I will introduce the speakers for Commander Tsao, so he doesn't have to hobble up and down. I am actually in better shape than someone today. That is excellent.

The Use of Portable Field SQUID Devices

DR. COHEN: I just wanted to thank the organizers for giving me a chance to speak here. I am always terribly, terribly inspired when I hear people like Dr. Ling and people in the military hospital support system by the level of dedication people see to their work, and it is truly impressive, especially for a child of the '60s who walks in with a certain kind of skepticism about this. It is special.

The title that was posted was maybe a little bit different than the title I am going to show you here. I want to talk about ultra-low field devices for producing MRI. This is work done in collaboration with myself and my colleagues at the Jet Propulsion Lab in Pasadena.

I am going to go ahead and make some radical claims. So I will just go ahead and start with my conclusions.

First of all, I want to tell you that practical high-quality MRI is possible with imaging field strengths of 100 microtesla -- that is 10 to the minus 4 tesla -- with instruments that will cost well under $200,000, so competing now in the range of ultrasonography, without exotic siting requirements which are traditional with MRI, without exotic uses of cryogenic gases, and finally, that this is stuff that should be available in the near term. We understand ourselves to be pretty close now with the quality of images that we are getting.

So, to just briefly review the stuff that you already know, high-field MRI, for all of its wonders, has a large number of liabilities. These include the instrument cost, the problems of projectiles.

This is a little video that apparently is not going to show. This is just an oxygen canister finding its way into an MR machine. We have had history of people getting killed under those circumstances, and obviously in the circumstances where you are looking

at battlefield injuries, where you are carrying around metal with the patient, this is a major problem.

The cost of cryogens are a huge issue. There are problems as you go up in fields that the RF, the radio frequency signal, doesn't penetrate uniformly in the body, and it produces image intensity artifacts.

There are problems with chemical shift artifacts. Fat and water gets displaced, problems with the signal getting blurred because of the relatively short T2-star, and there are safety issues.

So, in order to kind of justify the statements I want to make here, I am going to give you three slides on basically MRI. MRI goes ahead and detects the signal through the magnetic moment of protons, and protons, when they are placed inside of a magnetic field, line up with the magnetic field and process within it. They rotate around it, and the rate of procession turns out to be proportional to the magnetic field. So, with higher magnetic fields, you get a higher processional frequency. These are the dominant and simple things in MRI.

The way that MRI signals are picked up is through detection of the rotating magnetization and through inductive coupling to an antenna, and it turns out that the faster that the spins are processing, the larger the signal. So you actually get two components which are important in producing the signal magnitude. One is that the larger the magnetic field is, the more polarization you have. The second is the larger the magnetic field is, the faster the spins process. Therefore, in principle, you should get approximately a quadratic change in signal strength as a function of field, and this produces, of course, a very, very large penalty when you get to very low fields.

So how are we going to pull this off? My colleagues and I have been working with superconducting quantum interference detectors. These are quantum-level detectors for magnetic field, and rather than actually looking at the inductive coupling from the rotating spins into an antenna, we are doing direct magnetometry. We are measuring the magnetic field directly.

These are devices that have a decent history right now. They are established. They are relatively easy to make way for technology devices, and I guess time doesn't allow me to really go into the physics of the SQUID, but they are run at superconducting temperatures, at 4 degrees Kelvin.

These are just pictures of the SQUIDs that are being made by my colleagues at the Jet Propulsion Lab. JPL has gotten interested in SQUIDs because of their interest in bolometry, in measuring milli-Kelvin temperature differences, and they can be used for this. They can be used for telescopes and whatnot, but they develop an enormous capability for building these devices. These are just examples of the SQUID wafers that they have worked on.

The SQUIDs are almost impossibly sensitive. This is the detection efficiency of these devices compared to some various kinds of biological signals. Evoked brain signals might be 10 to the minus 13, to 10 to the minus 14 tesla, and the SQUID is detecting down to about 10 to the minus 15. To sort of put this into a little more perspective, this is where conventional MRI lives, somewhat off the chart. We are many orders of magnitude away from it, 15 orders of magnitude.

Another way to put this at the lower end is the energy change detectible by a SQUID is equivalent to dropping in an electron by a millimeter under gravity, so enormously sensitive devices.

The way that we are actually going to go ahead and run these scans is almost like conventional MRI. In a conventional MRI, we actually do the scans inside a very large magnetic field.

In the SQUID-based MRI, we pre-magnetize the sample. So we have a period of polarization where we use an electromagnetic, not a big fancy superconducting device, and it only has to be on transiently. We polarize the sample long enough to magnetize it.

In our case, we are polarizing at .1 tesla, although we are ramping this up to .2 tesla. This is what gives you the magnetization signal. So the strength of the signal is proportionate to the polarizing field, not to the big magnet that you are in.

Then we ramp the field down in such a way that we can preserve the magnetization and do a relatively conventional MRI pulse sequence. Here what I have shown you is a 3D gradient-echo style sequence.

The device itself is almost impossibly simple. This is a picture of the actual device, and this is a schematic of it. We can see in our prototype right now, we have a single SQUID detector, which is coupled by a second gradiometer to the sample, and our sample volume right now is about this big. So we have our polarizing magnets here, and these are the gradient coils.

In the actual device, which was made by a postdoc, the gradient coils are here. They are just wound around a fiberglass former, and here is the SQUID detector. Here is a closeup showing the polarizing coils.

MRI has been moving along for quite sometime, and this is just a kind of a quick rundown of where we are with MRI for the past 60-odd years. The process was first discovered usable in the '50s, and the first images were made only about 30 years ago. These are examples of the first images by Paul Lauterbur. The first biological images, at least that appeared in the press, would have been those of Ray Damadian, and MRI was commercialized 20-odd years ago, and these are the first head images.

The clinical usage started to ramp up very quickly from there, and since then, MRI has just been zooming along. These are kind of the first functional images.

So here is where we are with ultra-low field MRI. These are our first images on the upper left in 2006, and these are cross-sectional images of a wrist, and then here as compared to a high-field imager. About 9 months later, here is what the pictures look like, and here is where we were the last time we collected data on this instrument. We have actually ramped it down now to go and build a large field of view imager.

So we seem to be moving along at a pretty good rate. These images are now resolved to 1 millimeter, and here are some other pictures, 30 years of conventional MRI and 1 year of how we are moving along.

This, by the way, is a 300 Bicron-resolved image through the phalangeal joint of the hands. So we actually have the capability to get good pictures.

One of the questions we worry about a lot is the properties of tissue at these very low fields, and it turns out that the relaxation rates, how rapidly things magnetize and demagnetize, is a strong function of field strength, and this is some plots we acquired just recently comparing the T1 or the R1 relaxation rate as a function of field strength, and you can see that the relaxation rate slows down very rapidly as you go up in field. This is very well known, although the datapoints at the very left end of this are new because people hadn't been able to do that.

The T2 rates, the transfers relaxation rates, are known to be relatively flat with MR field strength, although it turns out that in biological tissues because of actually the

similar properties that Dr. Kraus described, the observable T2 rates are relatively shortened by processes such as diffusion. So, in fact, there is a field dependence of T2 which tends to reduce the amount of signal we have available.

There is the R1, and this is the diffusion-related T2 rates. So, as you use a conventional MR sequence, the apparent T2 becomes shorter, and finally, the R2-star rates, which are the signal rate that is determined by the field in homogeneity and limits the SNR of the system, tend to get relatively rapid at high field. So these things, it turns out favor, all of them, low-field imaging because as the T1 times are reduced or the T1 relaxation rates are shortened, that means we have a more rapid cycling time of the magnet to get our pictures. As the T2 rates are decreased or the T2 becomes longer, the signal stays around for a longer time and allows us to lower the bandwidth of this system, which gives us an SNR gain.

So this can give us a little sense of what are the issues with signal-to-noise ratio in these scanners. The polarization field would now be, in our system, .2 tesla versus say 1 tesla. So that is a favor of 5 loss. The polarization time is going to be shorter because of the T1 effect.

The noise power per pixel is an extremely interesting issue here. It turns out that in conventional MRI, the dominant noise sources are thermal noise from the body, radiated body noise as well as eddy-current noises in the body, and at low field, at R field strength which amounts to about a 7-kilohertz imaging signal, there is no detectible body noise. We are absolutely at the noise floor of the SQUIDs when we are detecting the signal, and this gives us an enormous gain in SNR.

The bandwidth gains are substantial because we can lower the bandwidth down because of the long T2s, and we have a number of other factors that work in our favor.

In the interest of time, let me kind of summarize where we are with this. We get shorter T1s. We get comparable T2s. We get lower bandwidth. We get lower overall net noise.

All told, we have on the order of between 50 and 70-fold SNR to play with, compared to kind of the RF-based systems out there.

Practically speaking, the devices could be made extremely small. Our current device sits on a platform that is about 1-meter square. So we could actually field-base a system, that is, field base not in the sense that Dr. Ling was discussing probably, but into a doctor's office in about 6 square meters. The power consumption requirements are incredibly low. The weight is incredibly low. You can wheel this thing around if you needed to in a hospital floor.

There are some liabilities. The contrast behavior is certainly going to be different at low field. Whether it is better or worse I think is an open question. It is certainly going to be different.

It is probably not the case that we are going to be doing fMRI, the way I have already done fMRI. We will probably have to develop new methods in order to go this route, and certainly, we are not going to be doing spectroscopy at those fields.

So it is fair to ask a question, am I just breathing laughing gas, and so let me give you a little history of where we are with this.

The first prepolarized MRI experiments that were really don't practically by McCloskey, et all, and that is a demonstrated and very accepted technique. the notion of using gradiometer pickups for ultra-low field MRI has been around now for about 7 years, about 8 years I guess now, and developed by Seton.

John Clarke and Alex Pines, two of the very leaders in NMR, have done some important work in this area of ultra-low field imaging, and these are the pictures that got me most excited about this field, when I kinds of dropped my conventional approach and said now it is time to do the big new thing.

These are cross-sectional images of a pepper, but they turn out to have been resolved to well under a millimeter in those pictures, and t hen here is the first head images I have seen from a scanner like this. These were created down at Los Alamos National Labs. The one on the right here is a conventional MRI. This is the ultra-low field system.

Obviously, this is not the one I want to go to for my next brain scan, but this is developing work, and it is moving very quickly.

So where is this all going? Well, from our first images to the phalangeal joints, of the phalangeal joints to pictures like this is where we are really hoping to be. We think that the ultra-low field scanner has the potential for SNR and resolution comparable to a 1-tesla MRI system, and we expect to be there pretty soon.

So, in the interest of time, I am going to skip the background in TBI because I know that we are running behind schedule, and I know that you guys have all seen this, and just cut to the last couple slides. My goal was to try and get you back on schedule, Ken.

Let me just say these words. We know that based on the clinical literature that MR imaging and TBI is probably better than CT. It is better than CT in acute trauma, as long as you can get people in there, and it is better in the back end when we are looking at people who are back from the field. They are back at Walter Reed, and we now need to do serial imaging to look for progressive changes, diffuse axonal damage and whatnot.

Currently on our system, we are working on increasing the field of view to make this into a head imager. This is our new gradiometer coil setup, and an interesting feature of our new system, which we will have a whole head field of view, is that we have integrated a cryocooler into this, meaning you no longer need to use cyrogenic gases in order to make this thing work. It is actually just driven from a wall outlet.

How important is that? Well, it turns out that liquid helium that we use for magnets is a severely limited natural resource, and that the projections are that it will be depleted in the next 10 to 15 years.

The prices are increasing hugely. We saw 30-percent increases this year and last year for the cost of cryogens, and MRI accounts for as much as 25 percent of the uses of helium, at least according to the pundits in the industry.

So integrating the cryocooler is a big deal. We cut the cost of this system down. We make it field deployable. We think we are going to be able to power it with things like solar arrays.

With that, I will just close, and here are a couple of pictures. This is our concept drawing for what we hope these things to look like, and it should be that we can build these on a flatbed system, and it should be that you could be able to go ahead and do surgery under tomographic imaging with these devices because of the very low fields that we are talking about. So thanks.

DR. CURLEY: Thank you.

[Applause.]

DR. CURLEY: Our next speaker is Dr. Alisa Gean, Professor of Radiology, Neurology, and Neurological Surgery here at University of California-San Francisco, and she is the Chief of Neuroradiology of San Francisco General Hospital.

Portable CT Use in Evaluating TBI in the Field

DR. GEAN: I would like to thank the piano player.

DR. CURLEY: Thank you. I feel a little like Liberace here.

DR. GEAN: You don't dress like him, though, thank goodness.

DR. CURLEY: One of the interesting things that we will talk about in the panel period is the issue of metal fragments, the fact that so many casualties have the fragments in them.

DR. GEAN: I accept money from virtually anybody who wants to give it to me. I am on the Medical Advisory Board for NeuroLogica.

In neurotrauma, we all know that seconds matter, not just minutes, and we need a diagnosis ASAP if there is any mass effect on the brainstem that might need to be decompressed.

So enter the Ceretom CT or a portable CT scanner. Actually, the title that is mentioned in the brochure is incorrect. I noticed it said portable CT and ultra-low field MRI, whatever that means. So that is incorrect. Someone had a dyslexic typing attack.

So here is the portable CT -- that is one of my fellows -- just to give you a feel for the size of it.

So here we are in the ICU. You can see the patient's head is in there. Here we are in the elevator, in the hallway, and in the OR. It weighs about 700 pounds. It is mobile. It plugs into the wall, but it can operate on the battery. It is wireless. It can be used in many different venues. We can even use it in the ambulance if necessary. I wheel it around from time to time. It is seductive for several reasons.

It is easy to use. Dr. Ling mentioned it would be nice to not have to have a radiologist, but there are computer-aided diagnoses that are out there that can facilitate, expedite, and identify traumatic brain injury, and that is being worked on. So those software programs are kind of interesting, which may put me out of a job, to some extent.

This is proven technology. The stuff that we just heard is spectacular. Wouldn't that be sweet to have high-field MRI images without all the problems of cryogens and ferromagnetic artifact and the potential hazards if there is a radio [inaudible] body near the globe causing blindness? We saw the oxygen tank and the downsides of MRI, and there are certainly upsides of MRI that outweigh CT in certain respects, but at this point in time, the CT technology, which has been around, as you know, for many,many decades is really very proven, and it too has evolved over the years.

If you go back a couple decades ago, the CT scans kind of looked like Rorschach tests, and you can hallucinate a ventricle in there, but now you have really a lot of details and extraordinary spatial resolution.

It is better than MRI in some respects in terms of identifying blood. If I have got an acute, for subachronoid hemorrhage which is something we are seeing every once in a while in the blast brain injury patients and may be one of the reasons why the post blast vasospasm is a problem -- I think there's probably several reasons why post blast vasospasm might be a problem, but subachronoid hemorrhage is a lot easier to see on CT than it is on MR.

CT clearly is the imaging technology of choice for fractures. Complex fractions of the skull base, for example, you don't even want to go there with MRI, and you can see fractures of the frame in transfer cerium, facial fractions.

The IED explosions, I spent a month on Landstuhl studying the facial fractures, and this is clearly CT territory.

The other thing that is kind of seductive about the portable scanner, you will notice the field of view is very small. It is not for the whole body. It is for the head, the neck, the face, extremities, or a pediatric patient. You can just put a whole baby in there, for example. So some of these portable scanners are in the NICUs because it is a lot easier to have a scanner right there rather than transfer the patient with all the extraneous stuff attached to them. It is a lot easier to have it available right away.

Then as Ken mentioned, foreign bodies are a huge problem with IEDs. The cases that I saw in Landstuhl, I mean they were just right and left. In fact, we actually went to the OR and extracted a foreign body which was an isolated foreign body, but it was a good size foreign body, from the neck in a patient that we suspected spinal cord injury, and we needed to get an MRI to look at the spinal cord. So that problem cannot be discounted in this war, given the type of weaponry that we are seeing.

So I mentioned in pediatric patients or in patients in general, transferring a patient, moving a patient is stressful to both the patient and the people that are transferring the patient, and transferring a patient has been associated with a 30-percent increase in hypotension. One episode of hypotension doubles mortality. Therefore, if you decrease patient transport, then one is likely to improve patient mortality.

Look at this patient. This is how we monitor patients now with TBI. In Landstuhl, they are hooked up to everything, especially given the polytraumatic nature that we have alluded to a couple times.

You have got an EVD. You have brain tissue oxygen monitor, jugular venous saturation catheters, endotracheal tube feeding lines, ART lines, venous lines, and then you are also worried about the cervical spine. There is a lot of stuff going on here, and you want to be very careful if you are going to be moving this patient around.

So how do you transport this patient to CT? Well, you don't. You bring the CT scanner to the patient. So this is that same patient, actually, and this is one of my friends. We are scanning the patient in their room.

Similar, this is now to push it to extreme, but this is an ECMO situation in a child. You can see the child buried in there with all the tubes and lines attached to, and this is just to prove a point of just going to an extreme to prove a point.

In combat, civilian trauma is often polytraumatic, but not quite as much as combat trauma. The patients that we would see in Landstuhl, they would come in from the CCAT with the open abdomen, with the blast lung. They are intubated, their abdomens. They are single, double, triple amputees. They have got burns, and so they have got some inhalation injuries. They have traumatic brain injury on top of all this potentially, but there are so many distracting injuries. Sometimes it is tough to really assess what is going on inside the brain when you have got so many other things and they are sedated, and facial injuries, ocular injuries.

Given the polytraumatic nature, everything is happening at once, you want something safe. You want something accurate. You want something easy, and that is another aspect of portable CT that seems potentially ready for prime time right here and now.

I want to show you how good the images are in the last few minutes. This is the portable CT. This is the current General Electric state-of-the-art CT. This is the portable CT. This is the current state-of-the-art multidetector CT.

The portable CT is a multidetector CT. It is an eight-slice scanner, which is only available in the last decade or so, the multiscanners.

As a neuroradiologist, I am genetically obsessive, compulsive, but most people would be very comfortable with the portable CT images, as opposed to the fixed large-bore CT scans.

Similarly, look at the bone windows. The portable CT scans at on the top. The heavy full-bore scanners is down blow, and it is comparable. It is very comparable, especially for fractions. You can do 3D rendering with the portable CT. You can do CT angiography. You can do CT profusion.

This is an interesting scanner that kind of stresses one of the pluses of the portable CT, and that is that any body habitus, I mean no matter what they weigh or their size or their shape, all you are doing is you are imaging the head. So here is a patient that couldn't be scanned. He weighed 500 pounds, and he has a very large left middle cerebral artery stroke, as you can see, but it is another plus that you don't have to worry about the size and the shape of the patient.

More clinical examples of the quality of the images, they are excellent. They are outstanding. This is just showing a stroke here in the left MCA territory. We have little extracts, a little hematoma here, a small amount of subachronoid hemorrhage shown in the sulci here, intraparenchymal hemorrhage here, cortical atrophy, and a big ventricle and a big non-hemorrhagic ischemic infarct there, good quality images.

Because we are concerned about the cerebral vasculature, especially, potentially in post blast vasospasm, CT profusion is an attractive aspect of this that can be performed, and here you can see CT angiography. Here is the right middle cerebral artery. You can see the left middle cerebral artery is missing, is occluded.

So these are some features that are ready for now, ready for here and now, and you can look at the neck, just to see if you are worried about something in the neck. This is noncontrast, contrast. You can see this necrotic node here in the right side of the neck.

The direct coronal imaging you can do, if you are looking at the paranasal sinuses, if you are looking at the orbit.

This is the portable scanner. This is the typical General Electric scanner, and here you can see some pacification of the maxillary sinus. Here it is very clear. It is a really nice demonstration of the anatomy.

So, to summarize the advantages -- and we can also talk about the disadvantages, which I would be happy to answer any questions -- it is easy to move around, and it is easy to use, unlike the patient which is not easy to move around.

It is easy to operate for both hospital and office personnel. It plugged into a 120-volt wall power, or you can operate it on a battery. It is very compact. It does not require any shielding of the room. It performs axial/coronal. You can also do reconstructions and 3D rendering. You can do CT angiography, looking at whether or not there is vascular dissections, pseudoaneurisms or occlusions.

It is compatible with multiple surgical navigation devices, which is why we use it in our operating room, and most importantly, it is best for the patient, less so for the physician and the staff.

So that is an introduction to portable CT, and I would be happy to answer any questions. Thanks a lot.

[Applause.]

DR. GEAN: Yes.

ATTENDEE: Dr. Gean, how do you move the patient from the scanner or move the scanner across the patient? How do you get that lined up at their bed or whatever?

DR. GEAN: There is a board, a flat board about so long that fits right into the scanner. So you do move the patient slightly. You move the scanner to the head of the bed, and then you put the sliding board right underneath the patient. Then on a one, two, three, you go about this far, about a foot to put them in the scanner. So you do need a little bit of patient movement.

ATTENDEE: Then during the scan, the scanner itself moves internally, the patient doesn't move?

DR. GEAN: Yes. The patient doesn't move. The scanner moves, the eight-slice, multidetector scanner. It is very cool. It is pretty remarkable. I wish it had some of the strengths that MR had because, frankly, if I could have both, this is better than MR for fractions, as I said, which is very important in polytrauma, but MR is clearly better for deep white matter lesions, if we are really looking at the detail in the future. DTI is not really ready for prime time yet, with normative databases and things like that, but if we are looking with vision to the future, to have that portability in a portable situation would be the best.

Other questions? Yes.

ATTENDEE: [Inaudible.]

DR. GEAN: I don't know.

ATTENDEE: [Inaudible.]

DR. GEAN: A portable whole body CT scanner?

ATTENDEE: [Inaudible.]

DR. GEAN: It was probably pretty large.

ATTENDEE: It was.

DR. GEAN: I mean, you saw it.

ATTENDEE: I don't think it is made anymore.

DR. GEAN: I don't think so either. I go to the annual meeting every year. I haven't seen anything like that, but limitations of this too is it is really just for head, face, neck, extremities. It is not body. It would be nice to be able to have the whole body, of course.

There are limitations to everything, but there are pluses to some things, too.

Yes.

ATTENDEE: [Inaudible.]

DR. GEAN: That is correct.

ATTENDEE: [Inaudible.]

DR. GEAN: Oh, the portable body one, you are saying? I see. NeuroLogica, the company with whom I am consulting is also a Massachusetts company.

Any other questions?

[No response.]

DR. GEAN: Thanks.

[Applause.]

DR. CURLEY: Dr. Hielscher is Associate Professor of Biomedical Engineering at Columbia University.

Study of Cerebral Functioning with Near Infrared

DR. HIELSCHER: I also would like to thank the organizers, Warren and Dr. Curley, for inviting me and giving me a chance to give you a crash course on optical imaging methods, which are probably the least developed at this point, compared to MRI and CT and the various other modalities.

I will jump right in and ask why can't we see through the body, and the problem was solved a couple of years ago in this movie where military scientists here in Washington, D.C., figured out a way to basically make it transparent.

Unfortunately, I haven't quite figured out how they did this, but this one gives a little bit away. The person put some water on his face, and we start to see him. Why is that the case? Well, water has a different refractive index, and whenever light interfaces between different refractive indices, you start to see effects like this. So it has a different refractive index of air and tissue, tissue of 1.4 and water of 1.33. So you start to see this person, and as it evaporates, the water disappears, and the person disappears again, but that is only one piece of the information that we need.

The other piece is we have to look at the structure of tissue, of what the different sizes of structures in tissues would be. Their membrane is very small, 10 nanometers, to cells which is about 10 micros, and everything in between.

If we now look at the wavelength of light, it is about 650. I also have a green laser here which is about 550. That is in this range, and waves that encounter structures that have the same size will be scattered. The major scattering comes from this range.

If they are smaller membranes, basically the light just travels over, and the larger structures, it bounces back, but scattering occurs on these structures in this range.

Early in the mid '90s, what has been identified as one of the major scatterer is a mitochondria which is about 500 nanometers in diameter, other typical structures like collagen fibrils, or if you look into the brain, you have nerve fibers which are composed of these axons, which again fall in the range of wavelengths where a lot of scattering is actually occurring.

So what is absorbing the tissue? Well, basically, everything. It is from the sugars to DNA, RNA, various amino acids, or with the enzymes. Everything has some sort of absorption spectrum. Here is one shown of the amino acid tarsen, and the spectrum is actually pH-dependent. So you can also gage other environmental -- or depending on what environment these chemicals are found, the shift of a spectrum will occur.

The most important one we are dealing with in the brain is actually blood or hemoglobin and the oxycomponents of that, which have a different spectra. This is the oxyhemoglobin spectra. This is the oxyhemoglobin spectra. This is the wavelength. This is what is called extinction of coefficient.

If you look at that, you see there is actually very large absorption in the visible. Here is water absorption, and then this explains. If you are trying to run a laser through a finger, it is red. You would expect that. A student may ask what would happen with a white laser, a white light source. Well, it is still kind of reddish. If I do a green one, you see nothing is coming through, even though it is much brighter than that.

It is basically this window where light goes through the red light. The infrared light penetrates the tissue very deeply, and this is often used now to determine exactly the deoxy and oxyhemoglobin. Because they have different spectrum, I can take two wavelengths, let's say 700 nanometers and 800, and now I have both wavelengths, measure the absorption at one wavelength, the adoption of the other wavelength. It is composed here of this extinction coefficient that you just saw times the concentration of deoxyhemoglobin and oxyhemoglobin, and the second wavelength also. So these concentrations are the unknowns. They are the same, but the extinction coefficients are different, as you saw.

These curve. From that, you can determine oxy and deoxyhemoglobin, and if you have more wavelengths, you can go to cytochrome or possibly water. Basically, you are limited there in the number of wavelengths that you use.

If you apply that now to brain imaging, you can actually show that light penetrates the scull rather nicely, and you can now look at the cortex. The depth that you are probing is about half the distance that you are separating. So, if you are separating your source and detector by 4 centimeters, you may go in 2 centimeters. If you are at 2 centimeters, you may go in 1 centimeter. It is the most likely path. So it is not one path, but photons travel, are scattered around, and there is the most likely path here.

There are different modalities that you can do this, and I want to start out here with the topography that is an example that my colleague, Professor Franceschini at Tufts University and now actually at MGH-Boston, which are finger-tapping experiments.

She just placed sources and detectors on the motor cortex and did not a tapping experiment. So this is a rest period. At some point, this would change to tapping, and these are shown changes in oxy and changes in deoxyhemoglobin, and the tapping occurs now. You start now to see these change sin oxy and deoxyhemoglobin up here.

These are surface maps, and they have certain limitations. I won't dwell on this, but first of all, they actually look at changes of oxy and deoxy and not absolute values, and the reason -- and if somebody has a question, I can go into more detail on that -- is you can measure changes at least 10 times with higher accuracy than absolute values.

The other thing is that you use very simple models of light propagation, and so if you have a source and you have a detector, you measure between them a certain absorption. You drop the fraction of the absorption in all. You have here a source and here a detector, and you measure between this absorption. You drop certain absorption parts on this grid, and then you get these maps.

What is much more desirable and many groups are working on it is the tomographic approach. You want to have a 3D model of light propagation in your brain and actually have a 3D resolution of that.

Here I will just show you an example where you have placed the sources, these positions on the forehead. This is a typical head gear that you can use, and now you shine light in here, for example, and you measure the different positions.

In order now to do the reconstructions, what you use are model-based iterative image reconstruction schemes. So you have the model of light propagation in your forehead that, for example, looks like this. There is a finite element grid. You have certain theories, the fusion models. You shine your laser in here, and now you assume a certain distribution of absorption and scattering inside your head, and you predict now what you would measure on the surface.

These predicted detector readings, you compare to actual measure readings, and you do some sort of analysis on that. For example, just look at this difference. You get an error value, just as a number. If this is smaller than a given value, you are done. If not, then you change now your internal distribution of sources and scatters inside your brain. You apply again your calculations and so on, until you have final results which shows you there is an absorber or there is a scatter in my brian.

So just look at the traces. These are now the traces that you get from the forehead measurement. There is one point where I shine the light in, and I measure now 13 traces in this case. In this case, I do a valsalva maneuver. I see these drops in absorption in the signal because basically the absorption is increasing. Then if I zoom into this first period,

I see all kinds of effects that I can observe. Now I will take these different time points, and I can now do dynamic measurements, which is really a unique characteristics I think of optical techniques.

For example, I can now look at very high rates, actually, in subsecond intervals. I can look at deoxy or oxy or total volume distribution inside the human forehead.

Some studies have gone on in the human head. There is much more work, and I just want to touch on that in small animals because you have much better control, and still the technology is at a stage where a lot of validation needs to be done.

In this case, I actually have here a small probe where you are going to have various sources and detector fibers which we place on the head of a rat in this case. So the blue points are the detectors, the red points are sources. You can start with simple things like carotid occlusions, and what you see, you can do a right occlusion or left occlusion, and it will affect different hemispheres of the brain, and you can see different oxy and deoxy and total hemoglobin values, which all makes much sense.

Other things to look at, forepaw stimulations where you now see much smaller effects, about a 1-percent change in the signal. So, again, these are 12 traces of the 12 detectors that are sitting on the rat's head, and this is normalized to 1 here. Then you see small, 1 percent change in the signal. You can take these changes now and, again, do your tomographic reconstructions of different parts of the brain, and you see things that are very similar to functional magnetic resonance imagine where you see changes in oxyhemoglobin, but we can also do this with deoxyhemoglobin and total blood volume.

This is a publication of 2006 here. A colleague at the University of Washington, Joe Culver, they have now a full array on the visual cortex where they have different types of stimuli, and now they see here, these are actually maps of oxyhemoglobin changes in the different parts of the visuale cortex, depending on what type of stimuli is presented.

These are just images at some time point, but again, you can see these measurements very fast. We can trace out actually these events, how they happen here over a 30-second time frame. The red one is the oxy. The dash-1 is the total hemoglobin changes at a certain point at the back of the head.

I want to touch a little bit on the instrumentation. There are three modalities that you can operate optical imaging on. The one with the most information, you have a time domain measurement where you shine in a very short pulse, about a nanosecond or shorter than that, and you look how that pulse comes out at different parts of the head, and it is typically broadened up to several nanoseconds, and kind of the peak arrival time and the width of this curve gives you information about absorption scattering.

A somewhat simpler version is frequency domain where you just now modulate your light at about 100 to 500 megahertz, and you now look at the face shift and the decrease in amplitude.

The simplest technique is the steady-state where you just shine constantly light into your brain and just see how the intensity drops.

The information content, as I said, this definitely has the most information. This is basically an integration of that signal, so the lowest information content. However, the price tag also goes up to about a million dollars a system to 100K for these systems. The data acquisition rate in the steady-state domain, you get several images per second. With this one, you have to integrate typically sometimes over minutes. So you cannot look at fast

hemodynamic responses. You have to look at longer times, but you may get higher accuracy in the image that you have.

Here is one point which I think is rather dramatic. This is the cross-talk, and by that, I mean you have absorption coefficients, and you have scattering in the brain or in all other tissues. Here is the simulation. So you have an absorbing object and a scattering object. If you do CW measurement, meaning continuously shining light in here, actually some of these absorbing effects appear in the scattering image, and some of the scattering effects appear in the absorption image. So that will actually confound somewhat your results that you get in oxy and deoxyhemoglobin and other parameters.

The frequency domain, you start actually to separate these effects. Here is only the absorption in the absorption image and the scatter only in the scatter image, just some of the tradeoffs that you have to deal with.

So that system is about 5 or 6 years old. It is a prototype, basically benchtop, definitely not used in the combat scenario, but since then, the system really has to become smaller. This is, of course, the first one which you actually could push around, and this went now from an analog to a digital system, which is really about a third or the fourth weight of this system. It is really just this box here, and it is very easy to carry around. You easily could also make that a portable system, but you still have to do this as a hospital system that we have in a card.

So there are several companies that sell instrumentation, ISS and NIRx and Techen. They are all relatively small compact brain imaging systems. What may be interesting, there are also handheld props. They are not tomographic, but they are very simple. They basically have one laser here, and they have one detector there. This is a system that is used actually in ambulances. In this case, they did a study where they looked at hemorrhages or hematoma. So they just place that on one side of the head, look at the absorption that they observe, and then place it on the other side of the head and see if there is a difference. If there is a difference, they say there must be a hematoma.

What they find is that actually an 11 acute, 1 subacute, and 18 chronic hematomas. So they diagnosed correctly all the 11 acute ones in the field. The problem is the chronic hematomas. So this is definitely something I think you could use in the field and could use directly in combat, while the other systems are more applicable in Walter Reed or at some of the secondary tertiary hospitals.

I think I am out of time. So I will just leave it at that and open it up for questions, and I think we have a panel discussion after that.

DR. CURLEY: Thank you very much.

[Applause.]

DR. CURLEY: I would like to invite the panelists to come up. Dr. Seong K. Mun is Professor of Radiology and Director of the Imagine Science and Information System Research Center at Georgetown University Medical Center. We also have Ron Kikinis who is Director of the Surgical Planning Laboratory and Professor of Radiology at Harvard, and Dr. Larry Clarke of the Cancer Imaging Program at National Cancer Institute.

Dr. Clarke, we will start with you.

Each panelist will have 5 minutes to expand on their interest in this arena.

Panel Discussion I: Policy Implications

DR. CLARKE: Good morning. I am probably the odd duck here because I work in cancer research, and you may ask the question why I am here. I was asked to come here and present what NCI is doing in the context of taking technologies through the

translational process, and the motivation really for this -- I have been at NCI for approximately 10 years -- is that we do not see the advanced technology to get into the clinical trial setting on a scale, on a timetable that is necessary.

We have over the last several years examined this to see if there is some means to try and address this problem.

One of the first things we have noticed in the imaging field is the platform dependence on how you collect and analyze data. It doesn't matter what it is MR, PET, CT, CT or ultrasound, or even optical. So there is a serious problem in the need to try and harmonize the collection of the data, as well as analyze the data, which is a big issue.

We are interacting with our colleagues who work on DICOM, and fairly recently, there has been a DICOM 23 compliance that pushed the idea of open architecture for plug-and-play tools across different imaging platforms. There is actually a couple of companies who are looking at this, trying to seek FDA approval of an open-source architecture for data collection and data analysis that will bring some rhyme and reason to how you collect and analyze data.

Also, NCI engaged several agencies of the Federal Government and worked with NIST on a recent workshop where they brought all the stakeholders together in medical imagine to really address how we address this problem of data collection and data analysis, and the clinical model to drive this was imagings of biomarker because biomarkers have really become a reality, and there is still a question mark on that.

The market on size of market for images of biomarker will be several size that of imaging in terms of radiation therapy, and yet there was a critical need to bring all the industry stakeholders together to try and get some harmonization across the different commercial platforms for data collection and data analysis because imaging should not be the variable in measured drug response.

So what NCI started off with really is a way of trying to address this problem in a number of ways. We got our colleagues in ACRIN to look at how you harmonize imaging protocols, and that evolved over the last 2 years.

Also, at NCI, we are collecting data that are from ongoing clinical trials and making that data available as a public resource and then trying to engage scientific and industry community to have access to that data and challenge them to come up with a consensus on how you train and test algorithms from that data. So then you try to harmonize or standardize, in a sense, image processing tools and data integration tools for data analysis.

We have also engaged in the scientific side just to take a leadership role. Very recently, the RSNA has got engaged in leading the other societies and meeting with the industry to put a pressure point on the imaging industry to consider how you harmonize data collection and data analysis.

Finally, I would like to just elaborate on one other area, which is that we have been addressing the issue of multiple modality imaging platforms where we have engaged the scientific and imaging industry, and I will just jump over this slide in the interest of time.

We have actually got a network. There is currently an optimal network, but it is moving towards a multiple modality network as of September of this year. What we are doing in this networking is scientific and industry partners that early in the technology development, to consider DICOM 23, to consider open science on how to validate these technologies, and they have an opportunity to see FDA approval in a shorter time frame. Although there is not a need for FDA approval for instruments used in the DoD sector, there is still a need to come up with ways of validating and translating these systems.

Thank you.

[Applause.]

DR. CURLEY: I would like to now invite Ron Kikinis.

DR. KIKINIS: So you acquire data, lots of data. You have a database, and all the data sits in the database. Now what's next?

Today, often we take a radiologist and have the radiologist analyze the data. The problem with that is if you have a lot of data, the model is not scalable easily because training radiologists takes time and is costly. So developing tools to allow the radiologists become more effective in doing large amounts of data and making some of the data interpretable by non-radiologists with very powerful tools is an area where there is a lot of potential. That is one aspect that I would like to talk about.

Again, this is research. So there is a lot of NIH funding going into this effort.

So the problem is how do you convert data to information. That is really what I think is an important topic.

Just as an example, the DTI data that we heard about earlier today, this is how a DTI acquisition starts out. What you have here, each of these slides actually represents an entire volume of data, and in this particular example, we have 15 acquisition directions. What you can then do is take all of this data and convert it, the complicated formulas, into simplifications.

We heard about FA, fractional anistrophy. I also have trouble with the word. FA is essentially just a long access of this ellipsoid. So there is much more data there that we saw, if we are restricted to FA alone.

Today, in clinical available systems, that is the leading edge of what is available, but when you go into research mode, you can go way beyond this. In tractography, you take the information that is in a single voxel and connect them together by jumping from one voxel to the next one, and then once you have those mathematically constructed tract equivalence, you can organize them using higher level statistical approaches, so that you can get to this type of this place, more or less automatically, but as was said during the presentation, now we need to turn these beautiful little images into something that has a quantitative measure where you don't necessarily need the radiologist on site to do the analysis.

In this example, today DTI is clearly a research method, and before we have much better analysis tools, we will not be able translate from research to clinical routine, and I think the same is true for many other methods. fMRI is finding its way into the clinical domain, but there is still a long way to go. We have heard in the presentations earlier today, the other potential methods also in early research stage really.

So what we are doing is developing software to do this post processing. We have chosen an open-source approach, free open source, and we think that for research and translational activity having an open-source platform at least is very important because it allows the free exchange of software and concepts between different sites. So it enables multi-site collaboration, and if the platform is not impeded by IP issues, it is suited for both research and commercial use. It doesn't prevent having a patent to technology to add value to the commercial activities, but the platform should be really open source, without IP restrictions.

The next work that we are working on this particular aspect is, as you see also, a national network, not just local.

I saw Larry's image. So I figured I would bring one, too.

Okay. Thank you.

[Applause.]

DR. MUN: Good morning. I would like to thank Dr. Grundfest and Dr. Curley who organized this very interesting symposium, and I appreciate their invitation.

I do bring a slightly different perspective in terms of historical things that we have been doing at Georgetown in support of Department of Defense.

When we had the first war in Iraq, Desert Storm, I was part of a team that took the very first CT scanner to the battlefield. In fact, it is really military that was the first that we knew at that time who pioneered the use of CT close to the battle zone, and at that time, we had a very crude method of transmitting CT images back to San Antonio.

Then when the United States military became a peacekeeping force for Bosnia, we established the very first, I think, global teleradiology service linking CT capability, as well as a computed radiography capability from Bosnia and linking to another combat support hospital in Hungary, and images were sent to Landstuhl for primary diagnosis.

In fact, some of the questions we were trying to deal with at that time, would you believe can we actually do digital imaging for chest films, then can we actually move this type of images over high-speed network for primary diagnosis. So we got to learn quite a bit about how certain type of patient care activities are conducted in different parts of the health care system, or in DoD, they call it "different echelons of care."

We had a very interesting presentation about portable CT. About that time, we did work with a portable CT that was manufactured by a company in the Boston area. The CT scanner at that time, the image quality was rather poor, and the throughput was rather poor. So we found that to be impractical. This was about 10 years ago, and this is when Colonel Vandre was involved in some of the projects that we were doing.

Now I would like to talk a little bit about the various types of injury models of brain trauma because unless we understand the injury models at various levels, we wouldn't know what kind of imaging capabilities we should deploy because different injury models and different types of injuries that take place will have different signature or signals, so to speak.

I understand that the TBI issues are somewhat different this time. The Department of Defense has been involved in trauma studies for many, many years. In fact, there is a huge amount of data within the Department of Defense among some of the research partners, but what I am learning is that this time, the blast is much more intense, maybe ten times more intense, and some soldiers are exposed maybe more than once. Therefore, some of the old injury model studies that the DoD and the civilian community conducted may not directly apply, and because of the severe intensity of some of the blasts experienced, the different parts of injury mechanisms may play a different role.

Certainly, the brain could experience a severe acceleration and certain way will penetrate into the brain and skull could be deformed, and there could be a significant amount of cavitation because of intensity of the blast, and this could produce a different type of injuries in the tissue level.

Again, many of us are familiar with what type of injuries the tissue would experience, but in this case, maybe there will be a different distribution of injuries compared with the traditional concussive injuries from football games or rugby games.

Because of that, the damage we experience at the cellular level could be very different. Then, of course, there is the molecular consequences of those kind of injuries.

Then these molecular consequences express themselves in a manner that may or may not be detectible, or in some cases, we might be able to detect it right away. In some cases, we might have to wait weeks or, as somebody alluded, maybe a year or so.

So what sort of detector or imaging capabilities we bring to the table to address the question will largely depend on our better understanding of injury models at different levels. I think this is where there seems to be a significant gap, not because we haven't tried, but I think largely because the type of exposures, the intensity of exposures are very different than what we are used to.

There are many different types of imaging techniques, and I think more will be discussed later, but we do have to see what sort of a signal we are trying to pick up, but you know, when it comes to imaging, signal is not good enough. You have got to have a signal-to-noise ratio, and also, you have got to have a contrast in order to see these things. So we have to be concerned about, let's say, the intensity of the signal and/or the lack of intensity of signal outside of the area of interest.

I would like to say a little bit about that this is a session that deals with the policy. I am not a policy expert. Once we understand what sort of imaging capabilities will answer some of the basic questions we are trying to address, we also have to understand when do we do these kind of studies. Just because we can do it doesn't mean we can put everything in the combat support hospital. Also, what are we really looking for at that stage of the game dealing with the wounded soldier?

Once we get the information, well, somebody said we don't want radiologists. Well, it is difficult to get radiologists to certain areas, but who is going to use that information, for what purpose, and when should the intervention be applied to have a better outcome?

The other issue that we talked about is perhaps we should look at beyond just the brain. What about lower brainstem, and what about the spinal cord? There are some indications in some of the work that we are doing at Georgetown University that seem to indicate the lowe brainstem may be a very important area that we might need to look at.

Thank you very much.

[Applause.]

ATTENDEE: Thank you.

We would like to open up the floor now for discussion. Before we do that, I just wanted to clarify one thing. I may have misheard you, Dr. Clarke, during your presentation, but from my understanding, all of the technologies that we will develop have to have FDA approval before we can take it out to the field for the military.

DR. CLARKE: I wasn't sure about that.

I should mention when I was talking about the network in the context of FDA approval, it is that the network is not a self-organized network that we have for multiple modality imaging. In fact, it actually addresses the problems that Seong raised, that we are asking the investigators to define a cancer problem and develop an imaging platform to address that problem and optimize that platform specifically for that application. So it is not just one modality. It is multiple modalities.

So the idea there is almost sort of a religion in the imaging community about being associated with one image modality. We are trying to get away from that, but the FDA and this scientist, as well as the NCI scientists, are on the steering committee, so that the open science approach is such that the FDA scientific arm understands the process and then in turn would help shorten the science that is required to get FDA approval. We can't

directly impact FDA approval, but it is open science towards the validation of these technologies with the FDA engaged and NIST actively engaged in looking at biomedical standards because NIST just recently has gotten engaged in developing standards for biomedical imaging. Then you create an open science approach where you may settle with FDA approval.

So my problem is I was understanding that in some instances, there isn't a need for FDA approval for DoD, again, in working cancers.

ATTENDEE: I believe most things do need FDA approval. I'm sorry. All things do need FDA approval for DoD.

Dr. Ling?

DR. LING: [Inaudible.]

ATTENDEE: [Inaudible.]

DR. KIKINIS: We know, for instance, from research in multiple sclerosis that goes back many, many years that subjective assessment by the patients themselves is a very complicated field to assess what is going on in the brain. Basically, DTI is one of the first non-invasive methods to do functional mapping of the white matter of the brain. That is good news.

The bad news is it is only now becoming practical which means that a lot of the basic research, the assessment of the ground line has not been done yet. Unfortunately, I think actually the soldiers that go into the war zones would be a good group to do scanning as a way to establish this baseline because they have a very high likelihood of being affected by those injuries. So, if you had the baseline, you could compare the individual soldier's scan to what has happened, and that will give us much better understanding potentially for what is going on there.

ATTENDEES: [Inaudible.]

DR. KIKINIS: Yes. And it will be with us for decades because those are all young people, and many of those people injured are injured, but that will not affect necessarily their survival rates. We will have large numbers of people for many, many decades. So having a good baseline will save us down the road a lot of headaches, I think.

ATTENDEE: Dr. Kraus?

DR. KRAUS: [Inaudible.]

ATTENDEE: I should also comment on that point that the DOD has money set aside for the specific study to look at post traumatic head injuries and epilepsy development and how to treat it.

DR. MUN: One of the catch phrases we used in a previous war, as Colonel Vandre knows, is fibromyalgia, and the fibromyalgia became a topic in an article recently because some pharmaceutical concerns are now marketing certain drugs, and there is a huge community saying that is not a disease, but when we looked at fibromyalgia as a result of the previous war, the same issue occurred because there seems to be about 3 to 4 of the general population has a symptom of some sort of a fibromyalgia, however you define it. Some people say it is some pain of unknown origin. Then how do you really separate that out from that of the war-related injury or war-related impact? Noise ratio is very poor in that area.

ATTENDEE: Can everyone in the back hear the comments from the audience?

DR. CURLEY: At this point, if you have anything else to add, we should probably wrap up.

DR. CLARKE: I have one just very brief one, and I think it is an important point.

NCI is facing the question of therapy response over time, and the question that comes up is how do you consistently measure change, how do you establish the baseline of what is the minimum change you can measure, which really I think is coming up here.

We are going to go through the process of going through every modality and taking repeat studies, take a patient on and off or a subject on and off of an imagine platform and gage in the scientific community and really exploring how do you quantify change and how do you determine minimal change because you need a baseline in order to make an interpretation. I think the same applies to brain trauma.

DR. CURLEY: Thank you.

I want to thank the speakers and the panelists from this first session.

Right now, let's all take a break and try to get back on schedule. Let's all reconvene at a quarter 'til 11:00, and we will begin the session on monitoring.

Program Session II

Monitoring:

Military-Current State of Technology and Challenges

DR. CURLEY: After getting back on schedule, we have gotten back off schedule, but Colonel Ling actually made a lot of his comments in his opening remarks. So he is not going to have very long to talk here for introducing this next session, and this is the monitoring session.

Geoff, do you have anything you want to say at this point?

COL LING: No.

DR. CURLEY: So we will just go right to it.

We will start with R. Daniel Ferguson, Principal Research Scientist from Physical Sciences, Incorporated.

Challenges and New Devices for Noninvasive ICP Monitoring

DR. FERGUSON: I am going to talk about some challenges for noninvasive ICP monitoring from my perspective which is not the perspective of almost everybody in this audience. I am coming at this from the viewpoint of opthalmic diagnostic technologies which is a very different kind of way to look at the problem.

Of course, noninvasive ICP monitoring is a very important and valuable augmentation of existing brain imaging and other kinds of modalities that are used. Basically, the gold standard for this right now is catheterization, and that does carry some risks.

So, if you could find a compact, low-cost, noninvasive device that could be used in a combat support role, especially something that could be used more routinely and more rapidly than MRI or CT scanning, that would be a considerable advantage.

Noninvasive methods, though, the rap against a lot of these devices is that they are relative, and you have some difficulty looking at the ICP, absolute ICP. I am not sure I am going to solve that problem today.

Certainly, there are some specific tissue and fluid mechanics going on in the brain and the surrounding structures that a better understanding of will lead to some signatures that we might find that will apply.

So optical imaging technologies have the potential to meet a lot of these requirements. I just wanted to give you an idea. I am going to talk about retinal imaging diagnostics, and I will give you sort of the big bang model for this. It started with digital

imaging technology that came in, in the mid century, last century, and then the scanning laser ophthalmoscope in the '80s became a very important imaging diagnostic for the retina, and then optical clearance tomography came on in the '90s, and then a variety of different techniques at the interfaces of these came in, including adaptive optics, and we added some of our own technology with line scanning imaging and with eye tracking to develop some powerful multifunctional diagnostic tools.

So we want to ask what from that universe can we import into this universe, and of course, a lot of the techniques, some of which you will be hearing about a little later, I think Dr. Dutton will be talking about some passive brain acoustic monitoring, and there is also, of course, ultrasound, transcranial Doppler, and in the optical world, other than the near infrared reflecting spectroscopy, which is not generally directly used for any kind of ICP monitoring, there is the technology such as ophthalmodynamometry. Of course, then there may be some advanced ophthalmodynamometry methods that may also be useful, and I will talk about those.

I will just talk briefly, very briefly about some work that I did, sponsored by TATRC a while back, which is a small pilot program, phase one, SPR actually, to demonstrate the existing retinal digital imaging technologies that are adaptable to ophthalmodynamometry, which I am abbreviating ODM so I don't have to say it anymore. ODM.

Just to give you some idea of the hydraulics of what is going on in the back of the eye, of course, you have the globe of the eye here, but the opthalmic artery and vein will pass through the optic nerve, about a centimeter back. They enter through the dural sheath and then pass on into the eye.

Of course, you can see the subachronoid space between the optic nerve sheath and the optic nerve, communicates with the cerebral spinal fluid, and so if you have an elevated ICP, you kind of have a tourniquet here, and you should be able to look at the modulation to blood flow in the eye to see it.

This, of course, is an old thing that was recognized more than a century ago and was looked at. What we tried to do was whether you could take one of our imaging devices, a new device that we developed with the support of the Air Force, for hybrid imaging looking at simultaneous OCT and SLO images.

The nice thing about the SLO images, even in this particular one down here, you can't see that the disk is obscured because it is off the field of view, but this system allows you to capture scans of the optical tomography scans of the eye and also wide-field images. Here is the disk over here, and you can use this kind of device for imaging, so that you can actually see pulsatility and things that are happening, spontaneous venous pulsations or induced venous pulsations.

So what we did was we took this device, and we modified it for ODM. I should go back quickly to remind you that the theory here is that the venous outflow pressure is going to be related to the ICP, which is this ODM pressure that you actually apply to the glove of the eye, which causes the pulsations, plus the interocular pressure. So that is the operational formula, and that is the fundamental theory of ODM.

So we have put this system together to show that you could actually put a load cell on the front of this and use a contact lens, so that you could apply the pressure, measure it, and see pulsatility, and this is just a panel showing a model eye. It is a poor image quality of a model eye, but you can actually use this load cell, and you can make this measurement.

You have to calibrate this for human eyes, and human subjects, we didn't go on to testing in this phase. We were just trying to develop the tools that you would need in order to go into the next phase of the study, and we came up with some interesting ideas about how you would actually integrate this in a field instrument where you put a Mainster contact lens and pull it off and then go to tonometry because the other thing you have to do with this is measure interocular pressure also to add in order to get the answer.

Then, of course, there are a variety of different modes you can actually look at with OCT at the optic nerve head and see papilledema and things like that. So there are some nice interesting things, but you have to have corneal contact.

So what are the limitations of this technology? Well, you have to have corneal contact, and that introduces some danger, especially in semiconscious patients who may be moving or having reflexes, and it is an instrument that has to be applied to the cornea. Because of tissue compliance and other things, by squeezing on the eye, you may actually change the baseline pressures. There may be other kinds of things. You need, of course, obviously, intact globes and limited blood in the vitreus.

So we looked at this technology, and we decided, well, maybe this is just too complicated. An ophthalmologist loves this kind of thing to do this with these multimodes, but to actually do the one thing that we need, it is sufficiently complicated that we were a little bit worried that this technology may not be the way you want to move forward for making estimates of ICP.

So we decided that we would go back to the well of opthalmic diagnostic technologies and see what is in the pipeline and what is happening. That was my learning curve about ICP, and now I am going to sort of offer you a hypothesis, too, for which we have limited evidence right now, but we think it is interesting enough that we should talk about it.

The objective here would be to demonstrate that recent advances in Fourier domain OCT technology can enable direct imaging of the subachronoid space, and that would be a shortcut in some sense to getting some information about what is happening in ICP.

If you look at the optic nerve anatomy, you will notice that there are the nerve fiber layers here. This is the optic nerve head and the main vessels, and then the layers of the retina are here, and then the choroid is here. Deep here is the sclera, and right in here in the sclera someplace is the termination of the subachronoid space. It is actually very, very close to the range of OCT, very close of standard 820 imaging. This was intriguing to us, and so we decided to look at what you would have to do to just push this technology just a little further.

The idea, of course, with ultrasound is that you can, of course, image the optic nerve head, but you have limited resolution. You also want to look deep in the optic nerve head because there can be some swelling above papilledema which is a chronic ICP indicator, but not a prompt, not a frank indicator of ICP elevation.

I just threw up some of these images to just give you a sense of the kinds of phenomenology you see with respect to the optic nerve sheath. It is known that in the case of ocular ultrasound, you can actually see an increase in the diameter of the optic nerve sheath, and that correlates reasonably well with some fairly high level of specificity above a certain threshold, but it is not, again, an absolute measurement, and you don't know whether they are starting with a big optic nerve. So it is somewhat difficult.

Also, there is some indication with elevated intracranial pressure that you can see sort of a scallion, an onion, a green onion-like shape to the optic nerve where the sheath is actually expanding and flattening the sclera at the back of the eye and creating a bulb right there. In fact, they find the largest diameter increased with intracranial pressure elevation is about 1.5 millimeters behind the globe itself.

So there is something happening right there. Also, the research that I have looked at, particularly German groups that did this with CSF infusions, discovered that this is an elastic response, and that the response is fairly linear, and it recovers very quickly.

So, in fact, it is well known that the optic nerve sheath in fact, does change its diameter in response to ICP, and there are a few caveats. The initial optic nerve sheath diameter is going to be variable, as the optic nerve is also, and the slope of these relationships has a larger range because there are some phenomena in the optic nerve, especially not the anterior portions, but farther back where the trabecular mesh changes the springiness, essentially, of this elastic response.

So there is some variability in that slope, and it is also nonlinear in the sense that it saturates at about 30 to 40 millimeters of mercury.

So there are some caveats here, but we think that there is good reason to believe that some geometry of that termination of the subachronoid space at the sclera may actually be a somewhat better indicator of ICP.

The hypothesis is, in fact, that that is exactly what will happen, that this angle, in a sense like a glaucoma where you have essentially the elevated IOP where you see changes in the angles in the very spaces in the anterior segment of the eye, you see there will be angle changes here at that point.

So the question is can we make that measurement, and I think the answer is that with recent advances in opthalmic imaging, I think you can do it.

Here is an image, an 820 nanometers of the eye, and you can see the correspondence of these anatomical structures here. What is missing down here is the fact that at 820, we can't quite get far enough. We are very close, but that is approximately where these structures ought to be.

Because the scattering curve actually allows you to get better penetration with longer wavelengths, I don't talk about the Fourier domain technology.

The idea is that this is, for example, some OCT images of a zebra fish heart beating. It shows you how much detail and how much fine structure you can actually see, which is sort of a very short penetration. Now we can increase that a little bit and get this kind of high anatomical detail in the back of the eye and use some of our tracking and scanning laser ophthalmoscope technology to actually lock onto the eye of a patient with sort of an articulated arm model, and then go in and make measurements deep in the optic nerve.

We are attempting to do this now, and I wish I could come here and give you the definitive answer whether this is possible or not, but the literature so far has shown the 1060. This is a very new, swept source, deep imaging, deep penetrating OCT technology. We have shown the possibility of doing image stabilization and averaging that gives you better detail at depth, but groups like Yasuno and now Jim Fujimoto at MIT with whom we are also collaborating -- we are not collaborating with Yasuno, but they have shown penetrating down to 2 millimeters. That is about how far we have to go.

This is all sclera. This is sclera down here. So that means in the optic nerve head, we think we are going to be able to see it.

The other key critical technology that you have to add into this is things like real-time signal processing, so you can do this in a compact package. We have been developing this kind of technology that goes along with these new swept source OCT systems.

Finally, we are right now at the cusp of doing our conversion of some of our existing TSLO units to do 1050 measurements and deep optic nerve imaging, and we are doing that now. We expect in March to have our first results. We are also doing TOCT tracking, optical instrument tomography measurements at MIT with Jim Fujimoto. So we have a couple avenues here that we are rapidly pursuing.

I hope to answer this definitively in about a month whether or not we can actually use this technology to see, directly image the subachronoid space. That would maybe be a new tack for tacking the ICP monitoring problem.

Thank you.

[Applause.]

DR. CURLEY: Thank you very much, and while I have the microphone, I would like to call on Dr. David Hovda, Professor of Surgery, University of California-Los Angeles.

Use of Biomarkers to Assess Cerebral Status

DR. HOVDA: I am going to talk to you a little bit about the neurobiology of traumatic brain injury, and as I go through this with broad strokes, I will try to refer to different types of components of this that could be used for biomarkers.

The cellular paradigm in traumatic brain injury, I am going to flash through these pretty quickly. Generally, if you can protect the cells, you can get them to work better, if you can stop cells from dying.

Another way to look at it is if cells survive the insult, the may exist in a state of dysfunction, much like you would think of concussion, and that state may affect their neuroplasicity recovery.

The other has to do if you just had more cells there, you could do more functions. The other part is that the cells may survive, but they may have to now adjust to a brand-new environment. The injured brain is a much different environment than the normal brain.

This is an old concept that was described as diaschisis. A lot of neurologists use this term now. Sometimes they use it inappropriately, but essentially what it means is that the areas that are remote from but connected to the side of the injury are dysfunctional for a period of time that alleviate over time, and it was coined by Von Monakow many years ago.

So utilizing an animal model of traumatic brain injury, you are using the lateral fluid percussion model. Yuigi Katiyama [ph] and others have described that at the moment of insult, there is a great increase in after-cellular potassium, very much similar to a wave spreading oppression that was seen originally by Layow [ph] and also described by Walker in the 1930s.

Also, there is an accumulation of calcium. This is an autoradiograph of a rat showing calcium flux which is light green and red, and this calcium actually will go for several days after injury. This calcium goes into the cell, creates some of the cascades of cell death or calpain activation that you will hear by others in terms of trying to pick up in terms of biomarkers, but this calcium low can happen in a piece of tissue that isn't dying, that hasn't shown any cell death at this particular time.

So what happens with traumatic brain injury, we know that all the cells fire. They discharge, and they release neurotransmitters. A particularly important neurotransmitter is glutamate. It binds onto the glutamate receptors. This causes a release of potassium and an increase of intercellular calcium and sodium. As sodium comes in, it brings in water, two things that kill people following traumatic brain injury, cerebral ischemia and edema.

This process of potassium coming out requires the use of ATP, to activate ATP pumps to bring them back in. When you bring calcium into the cell, it is bound on myochondrial. That is called an ATP loss. So you have a great need for energy to reestablish the neurochemistry following even a mild traumatic brain injury, but you have an inability to manufacture a lot of ATP.

So, without troubling you with the great detail, this is just a normal description of cerebral metabolism of the central nervous system, a blood vessel, a neuron, an astrocyte. You get two ATPs for each molecule of glucose that works on hexokinase. As it comes down, if you can get it to pyruvate and work in the myochondria, you get 36 ATPs. This makes it very efficient.

Most people, when you have models of ischemia or traumatic brain injury, you may have to live more off of these two ATPs which can perform lactate, and that is usually a marker of cerebral ischemia, and in fact, that is the case.

Here you take a 2 deoxy glucose image of an animal. This is an autoradiographic technique that looks at how much glucose the brain is burning, and at the same point during this particular time and minutes after injury, you can see this formation of lactate. So this is glucose that is burnt anaerobically, and lactate can come off primarily as a function of this burning of the fuel, but it doesn't represent cerebral ischemia.

This hyperglycolysis in the rat is now followed by a period of metabolic depression, which can last for up to 9 to 10 days, and then the animal begins to recover. During this time, the animal shows deficits that you can measure. One most important thing is it doesn't make any difference how severe or mild the injury is. The animal goes into these two states. It is the length of time that they stay in those two states.

So now you have a particular case where you have potassium, have an ATP mean. How about what happens with you have calcium and you have the [inaudible] mitochondria? Are there evidence for that ATP loss?

Well, here at the same time after injury, you have this increase in glucose metabolism and this decrease in activate metabolism, and most people that run an ICU unit will tell you that human head injury, they will show an arterial venous differences of about 50 percent for cerebral metabolic rates for oxygen.

If during this particular time of mismatch between glucose metabolism and oxygen, you also have a reduction in cerebral blood flow. The blood flow is not coupled. So now you have an ATP need with an ATP loss, and now you can't get the fuel to where it is supposed to go. Now you have metabolic crisis.

During this particular time, the animal normally can recovery from this without any problems, but if you have a second injury, even a mild second injury like cortical spreading depression, the cells go on to die, and you have permanent deficits.

The use of this fuel, we recently discovered is uniquely different, depending on the type of head injury. If you have a head injury that is a more focal injury, this is a neuronal phenomenon. If it is a diffuse injury, it is more astrocytic, and it is related to the glutamate, glutamine shuttle between the two cells that I can talk to at some other time.

But essentially, this idea is that this concept of metabolic dysfunction and glucose burning is dynamic. It is not related to consciousness. It is glucose metabolism that plays a role. It is primarily oxidative. There is a mismatch between coupling of blood flow to metabolism. The energy to manage a metabolic dysfunction produces an energy crisis. There may be an opportunity for metabolic therapy. Maybe we are hanging something wrong on the IV bag.

So what does this have to do with human head injury? Well, at UCLA, one of the things we do is a lot of translational research. So here is a patient that came in with a severe head injury. We did a PET study 2 days after she came in. She came in as a Glasgow Coma Score of 4. She was hypoxic for a period of time. These are the rates of glucose metabolism. Normally, normal would be right around green or blue, and she is hyperglycolytic throughout the entire part of her brain. She survived. She spent 9 years in a vegetative state before she went on to die.

So both in animals and in humans, you see this burn of glucose metabolism. This is the fundamental marker for all traumatic brain injury, and also after this burn, the brain goes into a state of metabolic depression, and this depression can last on the order of days to weeks to years for humans, whereas on a different order for animals.

Here is an example of the work that was published by Marvin [ph] in our group. So [inaudible] glucose metabolism. The brain goes in a state of metabolic depression and recovers over time.

This is what a normal PET study looks like, the burning of normal glucose. That would be mostly everybody, except for neurosurgical residents right after they are on call. Then they get a little low, but this is what a normal one looks like.

I had an individual that was a football player that had a concussion, and the physician, Jerry Fireman [ph], asked if I would like to study him, and I said, "I would love to study this person. Could I bring them in and study him?" At the same time, I have a severe head injury in. We kept him overnight. I asked him what the play was. I asked him who the President of the United States was. He was very interactive. He was worried about the combine. For those of you that are football junkies like myself, that is where they find out when they can be drafted for the National Football League. He was completely normal.

That night, I asked to see the scan of the concussion patient. They said that is the scan of the concussion patient. I said, "No, no, no, no, no. I need the concussion patient," because it was a severe patient that was done the same night. That is the severe patient. I said, "No, no, no, no, no. That can't be right." So whether you had a mild or a moderate or a severe head injury, you had the same response, just like the animals. The human brain would kick into hydroglycolisis and then go to metabolic depression.

The other thing that was interesting, it was just like in the animal studies. When we looked at white matter versus gray matter, all bets were off with the way the fuel was being used. If you want to be an expert in PET studies following traumatic brain injury, all you have to do is take a normal scan here, an actual scan. You can see the gray matter and the white matter, nice differentiation. Following head injury, you lose this.

You lose this primarily because the white matter has become dysfunctional in terms of its metabolic rates and diffuse head injuries.

Without going into great deal, just like in the animals where you have this high increase of glucose metabolism acutely and this reduction of cerebral blood flow, the same thing happens in human head injury, high glucose utilization, low cerebral blood flow, not ischemic but low. So it is mismatched.

This is a bit complicated, but here is how you can take different types of markers and combine them and come up with three or four different answers for different regions of the central nervous system following head injury.

These are NMR spectroscopies. These are done by Paul Vestivan [ph] in the ICU. These are the corresponding voxels that you see that are outlined in blue, and then we had two microdialysis probes here. These are the recordings on the right of extracellular concentration of glucose and lactate, glucose and lactate, and the corresponding PET study within the same patient.

So, with this particular voxel here, you have an increase in lactate formation. You have no extracellular glucose going on. Here is the lactate in terms of chemistry, and you have relatively good-looking glucose utilization. So the brain is burning this glucose anaerobically.

On the midline here, we have this particular voxel. We have no lactate. We have plenty of glucose. We have a little bit of lactate. This is about a normal level of lactate, and this particular depression of glucose is normal for the brain. This is a match which is appropriate, and then in this particular part near this contusion, we just have this hyperglycolisis.

This points to the second problem. We have a regional issue, as well as a temporary issue with regards to traumatic brain injury.

Now, if you look at this and you take glucose metabolism and you put it next to oxidated metabolism, the glucose-oxygen ratio should be about 5.6, 1 molecule glucose, 6 molecules of oxygen. You subtract those two images. You will have areas that show very low oxygen-glucose ratios which means that even though these areas here may not be hyperglycolitic and normal compared to normal amounts of glucose, it is hyperglycolitic for this particular brain because they are mismatched.

So, if you think of it the normal brain, 1 molecule glucose, about 5.6 for oxygen, you can have absolute hyperglycolisis, a lot of glucose being burnt, very little oxygen, or you can have something we would consider relative hyperglycolisis which a part of the brain would look metabolically depressed, but you are still burning much more glucose than you need for oxygen, and this would still form lactic acidosis.

If you have a normal brain or a person that is not in crisis, you could have a situation where a brain would come in, and it would have a low glucose utilization, but its oxygen would match. This would be matched. This would be a normal brain, a brain that would recover very well.

Then what we have is we have situations like this. This is technology that you can't obviously take out in the field, but in the United States and in many centers, you can do this now with positron emission tomography, glucose metabolism, blood flow, oxygen, oxygen extraction fraction.

I can take this image which is glucose and oxygen and subtract, put them on top of each other, and I can get a oxygen-glucose ratio. So I am looking for 6. Right? If it is lower than 6, it is hyperglycolitic.

So, if I do this, take my glucose and then take my oxygen, do the analysis, I can come up with an oxygen-glucose ratio, and lo and behold, I will have areas which are low oxygen-glucose ratio, meaning I am burning a lot of glucose and provided producing lactate, but then I have these areas of high oxygen glucose where the brain burns every molecule of glucose it has, and then it wants to burn something else. It has to burn something else.

What happens is we don't know what that burning is, but when we began to look at the arterial venous differences in patients following traumatic brain injury, we were surprised that, in fact, the brain not only takes up lactate after traumatic brain injury, but burns in.

Magestretti [ph] and others have described this particular type of phenomena in isolated vessels. Shure [ph] has done this before in the slice. Now the idea is that maybe what we are hanging on the IV bag is wrong. Maybe we should be hanging something that the brain would want to use.

Utilizing a particular technique with NMR where you can actually label the glucose, we now know that just like in the animal brain, the human brain is not burning the glucose normally. It is being shunted out to the pentose phosphate shunt, and it demands an extra fuel. That fuel primarily is pyruvate or lactate that comes in.

We also have learned that the human brain, just like the animal brain, can use ketones. If you give it beta hydroxybutyrate, it will burn it. It will restore the ATP production and will restore the survivability of cells.

This is an example of an animal we are looking at in saline and beta hydroxybutyrate, and this is an example of the human brain here where we actually measured the lactate and given the lactate and see that it comes out both in 02 and also generates ATP.

So the conclusion here is following traumatic brain injury, which gives us a very unique opportunity for biomarkers, is that we can't use the biomarkers that we assumed were right in the normal brain. The rules have changed. A biomarker which we think is for traumatic brain injury is probably not the same biomarker for stroke or another type of problem.

The fuel is dictated by the specific needs of the tissue, not by what we assume it needs. A comatose patient that has no epilepsy, that has a Glasgow Coma Score of 6, on a respirator, with all of the pain medication, under mannitol, is burning glucose enormously at a high rate, what you would normally see following in seizures, but you just can't see it because you haven't looked for it. It is not the amount of fuel perhaps, but the type of fuel that is really important. Glucose may be okay.

I think it was Dr. Ling or somebody showed a monitoring for insulin injection. We have always believed that you want to keep insulin injections there for head injury, to keep plasma glucose low. We know the head injury patients often come in with slightly hyperglycemic.

In a study that we reported with Paul Vestvali [ph], if you tightly control glucose and you lower glucose, you deprive the brain of that glucose, you actually show markers of cellular damage, glutamate will go up. The lactate ratio will go up. So the rules are different between traumatic brain injury and ischemia, and it gives you this opportunity for the idea of giving alternative fuels, like lactate or ketone bodies, and finally, it is probably never nice to fool mother nature.

That is my group.

Thank you.

[Applause.]

DR. CURLEY: Next is Dr. Richard Dutton, Associate Professor of Anesthesiology at University of Maryland Medical System.

Real Time (Acoustic) Monitoring of the Brain

DR. DUTTON: Good morning. Thank you very much for inviting me to come talk about my work. We all enjoy doing that. I am no exception.

I have the good news/bad news presentation. The bad news is I am right before lunch, and lunch cannot be delayed. I understand that, but the good news is it is a very smart audience, and a lot of what I need to say in background has already been said in one way or another. So let me drill right down quickly to the science that we are doing.

A couple words about me, I am the Chief of Anesthesiology at the Trauma Center in Baltimore. I am primarily a clinician, and the rest of my life is clinical research. I don't spend any time in the lab, and I don't understand a lot of the complicated science, but I understand brain-injured patients fairly well because I get to see a lot of them.

With the assistance of TATRC, right now we are building at the Trauma Center what we hope will be one of the most comprehensive brain injury research programs anywhere in the country, and I will talk a little about this as I go along, along with the specific project, the BAM, that we have been working on for some years.

So this is the big white box of chaos in Baltimore. This is the nation's largest trauma center. It is a freestanding trauma hospital. It includes its own admitting area, its own CT scanners, its own operating rooms, 36 ICU beds, and basically, when we admit a trauma patient, we own that patient until they are better.

This is my lab. This is Trauma Resuscitation Unit Bed No. 7. This is the team descending on a fresh admission. In addition to emergency medicine doctors, surgeons, anesthesiologists, nurses, many levels of trainees, there is a research nurse who descends on every patient as they arrive. Every patient admitted right now is a research subject. We get data from every one.

This year, we will see about 8,000 acute trauma admissions. The next busiest center in the country which is Miami, maybe about 5,000. 4,000 and some of these patients will have a brain injury, we think, if only we knew how to define it. You have heard a little about that. I will talk a little more about it as we go along, but we do somewhere in excess of 4,000 primary CT scans a year. So we at least thought they hit their head hard enough that they need a CT scan. The vast majority of them obviously are negative.

You can see the breakdown of injuries. This year, we will put in -- I don't know -- around 150 intracranial pressure monitors. We will do something on the order of 100 decompressive craniectomies this year, and we will have about 150 patients who actually die of severe brain injury.

One of my goals at the moment with the money we are getting from TATRC is to build a research infrastructure that lets us put every single piece of data about those patients in one place; a Brain Resuscitation Registry, as we call it. This includes pre-hospital vital signs, down to EKGs in enough detail to process them, for instance, for heart rate variability. It includes biomarkers obtained at admission, both the conventional ones and investigational ones, like the Banyan projects that we will hear about.

It includes brain acoustic monitoring in some patients. It includes obviously all of the radiology. We link to the Trauma Registry. So we have every bit of demographic and injury severity data on these patients. We can pull in data from ICU monitoring, brain tissue oxygen monitoring in those patients.

We follow up every patient now with a detailed survey. So the vast majority who get sent home with a mild brain injury, we call them back a week later. We go through a structured interview with them, looking at their post-concussive symptoms, looking at their functioning, and now a select group of patients that we are doing 3-, 6-, and 12-month follow-up after their initial injury, putting that data in as well.

We are using the ANAM system developed by the Department of Defense. It is a neuropsychometric testing system. We get that on selected patients at time intervals after their brain injury as well.

So TBI, functional diagnosis, how you're doing, any anatomic diagnosis which pretty much boils down to CT scan and clinical practice right now, there's a lot of other modalities we are looking at, but clinically, the money is in the CT scanner, and getting the patient scanned as quickly as possible is one of the keys to good outcomes in the severely injured patients.

Here is a current definition of mild TBI. You have seen one of these already. The problem, as has already been stated, is it is completely subjective, I had a period of unconsciousness, I was out for a little while, and we assume that equals a brain injury. Having no objective way to define this is extremely difficult and is one of the major research challenges right now. I will come back to this point.

If we could invent the ideal brain monitor, it would have some of these characteristics. It would obviously be noninvasive. We wouldn't have to drill a hole in the patient's head to get good information. We could use it for diagnosis and monitoring. We could carry it around. Anybody could put it on the patient and get a number, and it would be cheap. We don't have one yet.

But we started working toward this goal about 10 years ago, and I will do a little storytelling here. When I first came to the Trauma Center, I was previously at Bethesda Naval Hospital. I ran the operating room there in the early 1990s. If you look at my picture in the brochure, you may get some hint of why I got out, but I left the Navy in 1994 and came over to the Trauma Center where I have been ever since.

We have been working on this project since about then. One of the first groups I hooked up with there was a bunch of engineers who had been spun off of Lockheed Martin by the end of the cold war. They were acoustic engineers. They were used to finding submarines, but with all the Russian submarines tied up in Odessa, it wasn't very hard to find them after that.

So they got early retirement, and a bunch of them formed a small company, Active Signal Technologies -- it is based near Baltimore -- that was looking for medical applications for some of the science they knew. They hooked up with us in the middle '90s, and we started working on a number of projects.

One of the first things we started thinking about was a way to measure intracranial pressure noninvasively. We didn't actually get that, but that is where we started.

I sat them down and explained some things about the brain and how the brain works, and then they went off to the lab and came back with a bunch of ideas. I thought that putting a big set of ice tongs on the head to measure skull compliance was interesting. We never actually tried that one.

We did start looking at acoustic technology, beginning just with volunteers in the lab. This is simply active sonar, what they were good at. We ping. We listen. In theory, the density of the brain tissue in between ought to have some bearing on the signal, and we put some volunteers like ourselves on a tilt table and went from head up to head down very rapidly, and you could see differences in this.

So the BAM Mark 1, the first brain acoustic monitor, was an active sonar system where we pinged at the temples. We listened in the middle of the forehead where we could get good acoustic coupling, meaning we can get the sensor on the skin, and we listened. This was the device, and this was an actual patient in the trauma center. Being

noninvasive, we convinced the IRB of that in an early day. We were able to take it right into the ICU and start trying it out on people with brain injury. That was what I brought to the table.

Here is a frequency response of active sonar across a brain-injured patient, and I can tell you there were some differences seen between injured and noninjured, head up and head down. So there is something there, but we got sidetracked fairly quickly.

One day I was talking by the ICU as they were finishing monitoring a patient, and they had just turned off the ping, but they still had the listen turned on. All of a sudden, up on the oscilloscope, we got this great signal, and it looked something like this.

John Sule [ph], the engineer, says, "Hey, what's this?" I said, "Well, I don't know what that is, but that looks biologically relevant. In fact, it looks just like the arterial line," and I pointed. There is their A line. This has the same curve. This is something important. We need to keep looking at this.

So our project developed fairly quickly into a passive sonar system where all we did is listen, and the simplest way to understand what the BAM is, it is a digital stethoscope. You can take a digital stethoscope off the market and stick it on somebody's forehead. You won't hear anything. The technology in the BAM is in the sensor that lets you get down to micrometer motion of the skull reflecting what is probably the arterial pulse transmitted across the brain tissue, and that is what we are looking at.

This is a BAM signal, again, from a patient. It says Patient No. 18. This was one of the series of 30 that we did, our first project, and this was 5 or 6 days post injury in the intensive care unit, all patients with invasive intracranial pressure monitors, so all severe traumatic brain injury patients.

This person at this point in the midst of intensive therapy has an ICP of 4, and what we later came to recognize, a very good BAM signal. Here was the Mark 2 system. You can see the sensor here. Just a flat disk sticks to the forehead. We put it on with a little headband, to put a little bit of pressure on it to help your coupling, and a little signal processing box and a laptop computer running LabView. This is not very complicated technology.

This is what a good BAM signal looks like. Interestingly, of the patients we measured, that 30 patients, about 15 of them had a signal that looked like this. That is, it looks a lot like the arterial pressure trace. Those 15 patients all either went home or were discharged to rehab with a good functional status and a GCS of 13, 14, or 15, so all good recoveries from very severe brain injury.

This is what a bad signal looks like. You will notice the ICP isn't very different. The ICP is 12 in this patient. It is being intensively managed. That is what we do. That is what the Brain Trauma Foundation protocol calls for, but you can see that the BAM signal is very, very different. This looks very bad, and in fact, this patient was pronounced brain dead within about 12 hours of this picture. In fact, the 15 patients who had crummy signals that look like this all either died, about half of them, or left to rehab persistently vegetative.

Our next step in improving this was to torture the data a little more, and this led us to fast Fourier transformation of that time domain signal into a frequency domain. So this is the waves. This is taking apart that wave and looking at it. You will have to take my word for it. This is a normal BAM signal, and you can see a very smooth fall-off in frequency. Obviously, the fundamental here is the arterial pulse rate.

This is what a bad frequency analysis looks like, and again, this was a patient who did very poorly, but you can see a very chaotic signal, a lot more high frequency noise. What we think this represents is turbulent flow in the brain. So what we are looking at here is brain-blood flow, and what we are measuring here in the simplest approximation is laminar versus turbulent flow, smooth blood flow versus disordered or chaotic blood flow.

Here is the current system or a newer generation of it on one of my lab assistants, and you can see it is really pretty simple. The sensor is on the head. We now put one on each side of the forehead and get both sides of the brain. You can see the next addition here is a wrist sensor, looking at the arterial pulse. This is another way to get extra data out of it. We added this about 5 years ago. You can take the arterial pulse signal, capture it with the same technology, and then use that as a reference for the patient's arterial tree. It turns out in normal people, they are the same. The brain looks the same as the radial artery.

In abnormal people with a brain injury, the radial artery signal looks normal. Systemic profusion is normal, but the brain looks disordered, and you can capture this mathematically in what we call a subtraction analysis, but this is simply the subtraction of two frequency displays.

You see the black one here is the brain, and gain, it does not fall off smoothly here. The red is the radial artery which is more normal, and the blue bar is the difference between the two, and that difference turns out to be significant.

Here is the system we are working on now. We tracked it a couple years ago, a bunch of funding from the Air Force to basically take the BAM from where it was as an interesting research toy and operationalize it. It was a fairly large amount of money and a very ambitious project. We have completed some parts of it, not others. The BAM right now I will say is in the middle of 510(k) application process with the FDA. It is not yet approved, but we are in the middle of that track, and this is the current system running on a laptop in the hospital.

Right now, I have about 400 patients worth of data from the last 6 months in TBI patients, mostly mild patients which we are in the process of analyzing.

We have also as part of the military development gotten this down to palm pilot size. In fact, we don't have to add any weight at all to the medic's bag except the sensor itself because this will run on the same whatever electronics they are carrying, and whatever echelon of care you are, whatever electronics you have, this does not take a lot of space. It does not require a lot of computer power to run.

This is a hardened system for the Air Force. This one has five sensors on it. Because we were engaged in projects looking at different arteries around the body, to boil this down to brain injury, you really need one brain sensor and one reference.

We are working on developing a medic-friendly red, yellow, green system that says good, bad, reconsidered, and I won't drone through the process, but you get the idea.

Over the past ten years, we have enrolled about 800 patients now -- this has gone up since I put the slide together -- in various brain studies. We have studied it pre-hospital in the helicopters, the Maryland State Police. It does work in helicopters. You have to control for the vibration. It doesn't mind the noise so much, but we have had it in the Air Force's test chamber at Wright-Patterson as well.

It is very safe. It is completely noninvasive. It is a nonsignificant risk device which has made the research with it easier, and this is what we think we know scientifically.

We have put it on a lot of normal people, and we are doing another big run of normals right now as part of our current project, both completely normal people, those walking around the Trauma Center, and patients that come in as trauma patients but we think don't have brain injury, so two different normal control groups, and we are getting a bunch of that data. Normal people, by and large, have normal signals. Brain-injured patients have abnormal signals, and that is almost universal.

When we started this current project with the Air Force, we thought we would be able to discriminate mild brain injury from severe brain injury, and that there would be a bunch of mild brain-injured people who had normal BAMs. Not so. You hit your head. Your BAM becomes abnormal, and echoing what Dr. Hovda just said about energy metabolism in the brain, blood flow is disrupted very, very early at very mild levels of injury. So what we have at the moment is a very sensitive monitor for brain injury, the presence of brain injury. We are working on the specificity depart for the degree of brain injury. It doesn't do that well yet.

Abnormal BAMs post TBI is a bad thing. We haven't done a lot of recovery studies with it yet, but you do want you BAM to go back to normal, and the sooner, the better. We think we know that.

If you have a CT abnormality, so that is, what, 5 percent of patients with mild brain injury will have something on their CT, the BAM will be positive; that is, it will be abnormal for sure, and all the moderate and severes will have abnormal BAMs.

What we think we may have developed -- and when we look at the current batch of normals, we will be close to being able to say this scientifically -- we think we may have an objective marker for brain injury. If your BAM is abnormal, you are brain-injured.

Right now, we are comparing it to neuropsychometric testing. We are comparing it to symptom surveys at a week and 3, 6, and 12 months afterwards. We hope we will be able to say this with a greater degree of scientific rigor in the near future, but this is pretty exciting stuff, and this is what we are doing right now.

It does have a lot of advantages for the military, and for pre-hospital use, it is cheap. It takes about 10 seconds to get that signal. So all of the time is essentially putting the sensor on, turning the machine on, and taking it off. The measurement itself is 10 seconds of clip.

It is very easy to use. My 16-year-old daughter did a bunch of pediatric patients as part of her high school science project, good data from that, and it is quite durable in its present incarnation.

We think it is going to provide objective information about who is brain-injured and who is not, and we look forward to doing a lot more projects with it in the future.

Thank you very much.

[Applause.]

DR. CURLEY: Thank you. That's great.

ATTENDEE: [Inaudible.]

DR. DUTTON: We need to put it on a lot more patients.

ATTENDEE: [Inaudible.]

DR. DUTTON: As a monitor.

ATTENDEE: [Inaudible.]

DR. DUTTON: Correct.

ATTENDEE: [Inaudible.]

DR. DUTTON: Right. Well, the first question, what we are trying to answer right now is what you just said. It is prognostic, and it is simply can we hand this guy a gun, can we let him drive a tank or fly a plane. That is the first question.

How quickly it gets better and what it looks like as it gets better, can we let him back in the game, Ben Roethlisberger was extensively monitored with the impact system, had a concussion after his motorcycle crash, threw three interceptions the next week. So maybe he wasn't quite right.

We don't have enough data to know that yet. Probably, the key next study we need to do with the military is getting baseline measurements because there is no reason you can't do this to the troops as they deploy -- it is fast, it is noninvasive -- and then look at what happens as they are brain-injured and how they recover from that. That is what we are hoping to do.

The only thing I know that makes the signal better right now -- and I have very little data about this, and it is part of the Air Force project that we really haven't operationalized yet -- is general anesthesia. If you take that patient to the OR and anesthetize them, their signals all get better, not normal but much better.

ATTENDEE: [Inaudible.]

DR. DUTTON: I don't know the answer to that, but maybe we will find out. That is a great question, and it is our question, too.

ATTENDEE: [Inaudible.]

DR. DUTTON: Digital stethoscope. We can make this look very simple for the FDA.

ATTENDEE: [Inaudible.]

DR. DUTTON: It is an ongoing dialogue. We also have transcranial Doppler that you can look at. Now, TCD is a very different technology, single large vessel, operator-dependent. I mean, there is a bunch of issues with that. This is more a global measure, but the FDA hasn't given us any problem on that part yet. It is all about whether it does anything, and it is all on the efficacy side.

Sir?

ATTENDEE: [Inaudible.]

DR. DUTTON: Yes. Right now, we are getting to red, yellow, green, and we are just starting to test that, very crude.

I told the guys from the beginning, we all have the pulseoxymeter. It is a great model. I want one number, from zero to 100, that anybody can understand what is bad, what is good.

We are not there yet. We need a bunch more data. The real problem we have in the mild brain-injured population is what do you use as your gold standard for good and bad, and we don't have anything now. That is the real hangup.

ATTENDEE: [Inaudible.]

DR. DUTTON: It comes in a lot of different indirect ways. What we really need is a good PET scan study, but it is hard to put our population in the PET scanner early after injury, and we haven't done that yet. Other emerging technologies may help us with this; for instance, CT profusion studies as we are getting to fast enough, good enough scanners to do that.

Some of it is from mathematical modeling, what that looks like, how that should look.

Some of it is from data that is in the literature from animal studies and other TBI that shows early disruption of brain-blood flow after injury. Some of it is from looking at the radial sensor and how this response. There is a whole other aspect to this project that looks at shock and vasoconstriction, and as you vasoconstrict, your signals change. We can measure that much more directly in the periphery than we can in the brain.

So it is a bunch of indirect evidence right at the moment. One of the studies we really need to do is attaching it to one of these research methodologies that we are talking about today that will let us look at that directly.

ATTENDEE: [Inaudible.]

DR. DUTTON: Yeah. I think that is what we are looking at. It is a global measure. We think if you put the sensors all over the head, you could probably get regional information out of it, but that is way down the line right now.

DR. CURLEY: Thank you very much.

[Applause.]

DR. CURLEY: At this point, we will break for lunch, which is right out there in the hallway. Then we will reconvene at 1 o'clock at which time we will have the panel for the monitoring session.

As far as speakers and panelists go, I do have one thing for you to think about. The AIMBE folks would like to do what we often do at TATRC which is have a website dedicated to this meeting where we can put our presentations up. So, if you have any issues regarding putting your presentation up on the website, please let myself know or Mr. Rivkin, who you will see rotating around, know, and we can work on getting a scrubbed slide set, but we would like to do that, so we can sort of have a living record of the meeting here.

Thank you. Have a good lunch.

[Luncheon break.]

Panel Discussion II: Policy Challenges

DR. CURLEY: I would like to introduce our panelists for this afternoon. This is a panel discussion following this morning's monitoring session, and the panelists are Dr. Ronald Hayes, Chief Clinical Programs Office and Co-Founder of Banyan Biomarkers. David Moore. Dr. David Moore is Director of Research for the Defense and Veterans Brain Injury Center, and Pierre Mourad is an Adjunct Professor at University of Washington.

We will start with Dr. Hayes, and it is going to be the same format as this morning, basically.

DR. HAYES: Thank you, Ken.

I wanted to go over today issues regarding biomarkers, and since this is an engineering group, I wanted to focus on issues surrounding gaps in developing actually a device that would be useful in detecting biomarkers in a forward combat environment.

In 5 minutes, basically what I want to communicate to you is that under the auspices of RAD II and Colonel Vandre, we have with Frank Tortella and Banyan a program that is a biomarker assessment of neurotrauma diagnosis and improved triage system. It is a Banyan system. It is implemented, and the goal of this is to provide the infrastructure, if you will, ultimately for validation of biomarkers that would appear on a handheld device.

So Banyan was conceived several years ago by Frank Tortella and myself and others in his group to provide initially biomarkers to assess severe traumatic brain injury in the course of sever traumatic brain injury. So it embraced the discovery and clinical validation of biomarkers, including continuous assessment of physiological variables, I think as Colonel Ling has emphasized, that are essential in tracking the course of severe TBI.

So the clinical strategy in severe TBI, this study is underway. Our goal is to recruit 200 patients and appropriate control patients. We ar going to correlate to biomarkers with physiological parameters that are continuously recorded, as well as physiological, as well as clinical variables of injury severity, secondary insults, and outcomes. We have a number of sites that are now currently operational.

So Bandis [ph] is operational. There are a number of goals that we have already met. We have developed a protocol, three-tiered IRB approval, prepared SOPs. The sample tracking and data management is the first of its kind. There are more than 11,000 samples being managed in the Bandis protocols. It has never been done before. The continuous physiological monitoring on a study this large has never been done before.

We have completed our beta site assessment. We now have four sites operational. We are bringing on four more sites within the next month, and we have three backup sites. We have already collected data on 28 patients. Our goal is to have an interim analysis available at the ATAC meeting of three preselected biomarkers, and I invite further discussion of that.

We have recently received funding to expand Bandis which is really I think the issue in a combat environment is mild to moderate TBI, and the objectives were to develop the mild to moderate TBI protocol, to get approval by, again, a three-tiered approval process with Orlando Regional Medical Center as our site, Western DOD IRB, the conduct a pilot study and then identify additional studies for feasibility.

Really, the purpose of this study -- and I think it is very important to emphasize, and we can digress on this -- is can we detect the presence of mild to moderate TBI, can we discriminate between mild to moderate TBI, can we detect the presence, so against what do we validate these. So it is really the presence of lesions evidence on CT scan or prolonged deficits.

So we have a study group where we are looking at moderate and mild TBI. We are collecting a very robust frequency of samplings to look at the kinetics in blood of our biomarkers, and we have already achieved a number of goals. So the protocol has been developed. It has been approved by the DoD. It is under review by the Western IRB. Orlando will complete its review by March 15th, and we expect to begin the study in March. The data management system requirements have already been designed.

I am going to conclude my talk quickly by showing you this road map. It reminds me of sort of a self-signaling pathway, and people's eyes glass over at this, but it is to impress upon you the complexity of the road map to get FDA approval of a biomarker on a device, and it includes a number of components, developing assays, clinical validation, actually getting the device put together, and then getting FDA approval.

So the important point I want to leave you with is that Components 3 and 4 from an engineering standpoint, what od we need to do?

Now, we have funding for the feasibility of mild to moderate. Colonel Vandre has committed to that support, but these areas remain unfunded and unaddressed. We don't have identified a device or the antibodies to work with it. We don't have the funds to support pivotal studies for the FDA across the injury range, and we don't have studied to support GMP.

So, in summary, I think we have made very significant progress for developing the infrastructure for a handheld device to detect biomarkers for mild, moderate, and severe TBI. We need to rigorously examine, if you will, how we get across the goal line.

We are in the red zone, and I think it is time to think about how we actually deliver the beef here.

Thank you very much.

[Applause.]

DR. CURLEY: Thank you.

Next is Pierre Mourad from the University of Washington. Pierre?

DR. MOURAD: I am affiliated with the Applied Physics Laboratory at the University of Washington in Seattle, as opposed to your local and very big Applied Physics Laboratory, the lesser Applied Physics Laboratory as we refer to it out in Seattle, even though it is ten times the size, and also the Department of Neurosurgery.

I am going to talk briefly about some work on using ultrasound mediated palpation of brain to infer brain stiffness and I hope intracranial pressure, and I acknowledge some financial arrangements here. So, in principle, I am conflicted, but I don't feel conflicted.

We all know since we are talking about TBI here all day that the ideology of TBI is complex, and at the end of the day, these brains have contusions. They have hemorrhage. They have edema, and a significant majority of these patients have elevated intracranial pressure. As Colonel Ling emphasized in his introductory talk, ICP is a critical variable for patient management that is known in [inaudible] literature, and it is also known in the military, to find some way of measuring it quietly and noninvasively rather than invasively would represent a significant advance in triage out in the field, forward echelon patient management, as well as management during transport and in the civilian sector.

What we have is an idea where we would take ultrasound from a device for some stricken soldier such as myself in this case and place it at various places on the brain and extract the information necessary to infer stiffness and intracranial pressure.

So the basic idea is to take high-intensity focused ultrasound that is nondamaging, ultrasound that can come down to a point about the size and aspect of a grain of rice, apply it to various portions of the brain of interest, and since gray matter and white matter will probably respond differently to high palpation, that will take some of the research to figure out the appropriate part.

The hypothesis is that a study of the dimpling of the brain -- I will show you some pictures of that -- and infer the stiffness, and since ICP, we have evidence suggesting that ICP can itself change stiffness of brain. Anyway, we have that evidence. It suggest that if we can infer the acoustic properties of rebounding brain, we can infer intracranial pressure.

So here is an example of a rat brain that we have palpated with intense focused ultrasound, and we are able to measure it, generate a displacement about, in this case, less than the radius of a human hair. It comes back down in about 10 milliseconds, very fast, very quick. So, as much time as it takes to place such a device on someone's head, you would have a measure of their stiffness, and we have working with brain proxies in bottles that we can overpressure in various ways. It looks like we have meaningful indication that when brain at least in a bottle is subject to high intracranial pressure relative to low intracranial pressure, that the properties of the rebound, the focal rebound of that brain vary.

There are lots of things I can change intracranial, change brain stiffness, presence of edema or lack thereof. It is just one example. Brain age. My brain is starting to get real soft and [inaudible], compared to young people's brain. So I know that will be an issue. Nonetheless, at least for the military where we are mostly sending our young off to the

military, to the battlefield, I think we will be able to control enough variables to infer edema, infer brain stiffness, hence edema, and also I think intracranial pressure.

So my colleague Michel Cleo [ph] is a neurosurgeon. He and I are coinvestigators and coinventors of this technology, and we are hoping that it will bring something to the military that it desperately needs.

I will close by commenting on the three talks that I heard today because I think that is part of what we had hoped we would do. Excellent talks, of course, and very exciting technology.

When I listened to Dr. Dutton, I said given how easy that device is to deploy, except in the face of an IRB apparently, really that should be a no-brainer, no pun intended. I think he has a chance of getting that battlefield readiness, the battlefield readiness question which is a fundamental problem, of course, as people know here.

When I listened to Dr. Hovda, I said I want to throw away may ICP stuff and develop a portable, cheap, PET or SPECT device. That seems like the way to go to really help our men and women in uniform.

And finally, with Dr. Ferguson, he is months away, it sounds like, from having all the data one could ever want, the microanatomy of the nerve sheath, and he is going to find something very important there.

So thank you.

[Applause.]

DR. CURLEY: Thank you.

Dr. Moore? David Moore from the Defense and Veterans Brain Injury Center.

DR. MOORE: Good afternoon. I will just give my comments very briefly. I don't have any slides. One of my jobs is Director of Research for Defense and Veterans Brain Injury Center, headquarters at Walter Reed, a constituent part of the D-C-O-E, or DCOE, which is the Defense Center of Excellence for Psychological Health and Traumatic Brain Injury under the command of Colonel-Promotable Sutton [ph], Laurie Sutton. You may or may not be aware of that. It is certainly something that is being rolled out, and it is still in its formative stages.

I will make a couple of general points that occurred to me. In terms of actually developing a device, obviously we all know that you have to validate in terms of making a device or some sort of biomarker representative to a clinical population. Validation is the key.

I think one of the areas which maybe might be missed here in some of the actual attempts to validate these devices and also introduce them into the medical scenario is normal controls. There is a lot of good physiological data out there, that if these devices are truly noninvasive, you should be able to measure either diurnal variation, normal controls, pulsator variation in intracranial pressure. There is a lot of stuff out there that you can actually do to show an IRB, for example, that your device actually works. So preliminary data and normal controls and truly noninvasive devices should be really a no-brainer.

Okay. Thank you for your time.

[Applause.]

DR. CURLEY: Thank you very much.

At this point, we have a few minutes for some questions. The panelists can come up to the table.

I just would like to start off. I don't remember where I wrote my questions. I would like to ask Dr. Hovda, as far as the normalization of the mismatches in the PET studies, for example, that case with mild TBI where the scan was so profoundly abnormal, how long did it take for the study to normalize?

ATTENDEE: [Inaudible.]

DR. CURLEY: Oh, he had to leave? That is why I couldn't see him. I kept looking around. All right.

Then I would like to jump over to Dr. Dutton with respect to normal controls. Dr. Dutton? There is Dr. Dutton.

DR. DUTTON: Some of those PET scans, I have heard Dr. Hovda say that takes -- the extended abnormalities for 6 to 12 weeks.

DR. CURLEY: Really?

DR. DUTTON: Yes.

ATTENDEE: In some patients, it has gone as many as 14 weeks, and they slowly return, but they oftentimes don't even go back to baseline.

DR. CURLEY: And these are people that meet the mild characterization.

ATTENDEE: Football players.

DR. CURLEY: That is interesting.

ATTENDEE: The functional measure doesn't correlate as well as you had hoped with the PET measure then.

DR. CURLEY: No.

ATTENDEE: No, it does not.

DR. CURLEY: Obviously, some more needs to be done there.

Dr. Dutton, with respect to normal controls, do you have any work that you have done as far as that goes?

ATTENDEE: [Inaudible.]

ATTENDEE: So, as a comment to that, have you actually perturbed the normal patient in a way, such as CO2 inhalation?

ATTENDEE: We talked about that over lunch. That is right.

ATTENDEE: [Inaudible.]

ATTENDEE: Per our lunch discussion, you might be betting at vasodilation in those arterials, those secondary arterials, giving you perhaps something about cerebral autoregulation, and I know you know this. I am commercializing for you here.

You could get at some preliminary data, as you know, normals with manipulation. It is an excellent next step.

ATTENDEES: [Inaudible.]

ATTENDEE: I think that would be my question. So go ahead and start over again.

ATTENDEE: [Inaudible.]

ATTENDEE: I missed the first half of your comments. So I can't respond.

ATTENDEE: [Inaudible.]

ATTENDEE: I did care that you were talking to him, but I didn't track it as well as I should.

ATTENDEE: [Inaudible.]

ATTENDEE: So the question, as I understand it, is pick your right frequency in order to understand brain elastance, compliance. So, since we are essentially giving is an impulse, we are going across all frequency centered on the width, inverse width of the pulse.

ATTENDEE: [Inaudible.]

ATTENDEE: Watching the ring down, yes. In the brains that we have played with, not my own yet because I am not that gung ho, it just comes right back down to baseline.

ATTENDEE: Dr. Ferguson, one of the things about noninvasive ICP monitor, it has been really a Holy Grail for those of us in the services, and actually even practicing just straight old critical care.

Actually, the picture that Pierre showed of how you can do it right now, it is very invasive. I think anybody that thinks you drill a hole in the head, that would be in most people's mind invasive.

One of the things that you made a point about was that it is difficult to potentially get an absolute number, but you could get trending.

Something else, though, as you extract out the trending data, are you able to get a flavor for what the ICP waves would be like? Really, the ICP waves are actually very clinically relevant, things like A waves and B waves. Particularly, A waves are very, very relevant to us. When we see A waves, even though the absolute ICP may not be high, when you do start seeing A waves or plateau waves, you recognize that this patient is in pre-herniation state, and there are manipulations that you do to address them.

So one of the things that could be extracted out of the dataset, as I was looking at the way you were collecting data, might be the ability to extract out pressure waves.

ATTENDEE: [Inaudible.]

DR. FERGUSON: Our time scales are about 30 seconds to a couple minutes to get those plateau waves.

ATTENDEE: [Inaudible.]

ATTENDEE: The changes are usually someplace between 5 and 15 millimeters of mercury if you look at absolute numbers. So the patient might be cruising at, let's say, 10, and then all of a sudden, they start to develop an A wave. It might go up to 17 or 18. They sustain for a while or, as Pierre said, a couple, few minutes, and then it will start to come down again, but those are very, very pathologic.

ATTENDEE: [Inaudible.]

ATTENDEE: You would need to have the eyelid up to make that measurement, though. Right?

ATTENDEE: [Inaudible.]

ATTENDEE: The question about the whole variety of optical -- sorry -- opthalmic-based approaches -- God, I can't even say the word -- ophthalmologically based approaches to intracranial pressure as we discussed, a lot of them are TCITI [ph] based, and the biggest concern I have heard about them -- I don't know the answer to this fully -- is that when the brain is screwed up from some injury, one of the first places to suffer is the eye. That is, that collateral is going to get cut off before others.

So the question to the audience would be how often would you expect normal opthalmic dynamics, be it cerebral spinal fluid dynamics or blood flow dynamics in the case of TBI? I have no idea what the answer to that is, but when you move on with this, which I hope you will and I hope you have the opportunity to, of course, one of the questions will be what percentage of the population actually have normal enough eyes and its appropriate anatomy that you can apply that to. It would be an important question to ask.

ATTENDEE: I have a comment on the study in terms of how it looks in terms of when you are doing the biomarkers and in the face of therapy; in other words, the

changes of the biomarkers, quantitatively or qualitatively for that matter, in the face of therapy, because at the end of the day, again, what do you do with the data, and is the data going to drive therapy, in addition to diagnosis.

ATTENDEE: A very important question. One of the strengths of the program that Frank has put together is that the therapy that we would like to see, I guess it has been funded in part, to look at TBI has a biomarker component. So we are going to explicitly look at the relationship between biomarkers and therapy efficacy.

We have also been retained separately by other drug companies to look at the relationship between our biomarkers and therapy. So we will see that.

Now, our preliminary clinical data, preclinical data, indicates that is the case. Really, the final common pathway for cell death is highly conserved, whether it is through [inaudible] or humans. So biomarkers of cell death will probably reflect therapeutic efficacy in a general sense.

We are poised, really. What Frank's program has done is linked the biomarker development with the therapy development. It is actually a very occurrent approach called theronostics, and I think it was alluded to earlier in the talk where you use biomarkers to drive therapy development.

ATTENDEE: I have one question to that, briefly. So, when someone has polytrauma, more than just the brain is injured, how much did that confound your biomarkers?

DR. HAYES: A very important question. So the issue in selecting biomarkers -- and let me use Dave Hovda's talk as an example. Dr. Hovda gave I think -- and his group represents a pioneering and [inaudible] review of the potential of looking at metabolic derangements in the brain as signals for biomarkers of injury in the brain.

The problem is most of the biomarkers that we look at for metabolic derangements are not brain-specific. So, if you look at lactate changes or pyruvate or something like that, it wouldn't be brain-specific, and as we all know, traumatic brain injury is not a single. It is polytrauma. So you need to look at, if you will, brain-specific biomarkers.

So one of the criteria for our group in selecting biomarkers is the brain specificity and their robustness to confounds by polytrauma, but if you noticed in my very brief presentation, we include in the Bandis protocol, a polytrauma control. So we will look at polytrauma patients with and without brain injury to understand and to confirm or disconfirm that the markers are brain-specific.

ATTENDEE: I saw a question over there.

ATTENDEE: [Inaudible.]

DR. HAYES: This is really a great question because it allows me an opportunity to stress the uniqueness of the Bandis protocol.

The Bandis protocol obligates us to record continuously every physiological -- you know, the relevant physiological variables that determine patient outcome, and as Jeff Manley and others have published and shown, unless you record it continuously, if you take it off the bedside flow charts, you will miss it.

As for medications, we are in the process of really, frankly struggling with the amount of data that we get there, and at first pass, Clinipace Data Management System, we envisioned comprehensively embracing every medication and every dosage, and that has promoted challenges for us, but ultimately, what you will have for the first time in the history

of the study of traumatic brain injury, a comprehensive database set on TBI patients that will allow you to drill down into that.

DR. CURLEY: A question in the back.

ATTENDEE: [Inaudible.]

DR. HAYES: That is a very important question, and again, the Bandis protocol is addressing that. So you really have to look at -- there are three areas that the Bandis protocol addresses. That is acute injury, magnitude, and response. The response of the patient to secondary insults and intervention, at this point as Colonel Ling has emphasized, it is primarily management-related issues, and finally, it is outcome. So we will look at patient outcome.

If you were to look at our preliminary data published in the Journal of Neurotrauma about a year ago, we are able, at least with the [inaudible] Glasgow Outcome Scale, to predict outcome with biomarker levels just [inaudible] on Western blot and CSF within the first 24 hours after injury.

Now, the other important point is I think to look at these data in certainly a more granular fashion, and equally important is to look at the utility of biomarkers in the subacute and chronic phase and guiding rehabilitation. So we are also looking at that area as well. Now, it is not nearly so mature as our acute biomarker program.

DR. CURLEY: All right. Well, thank you very much. At this point, I want to thank our panelists and our speakers for this session, and we will take about a 10-minute break and get ready for the final session, which is therapeutics. So we will start the next session in about 10 minutes.

[Break.]

Program Session III
Rehabilitation Therapeutics:
Military-Current State of Technology and Challenges

DR. CURLEY: Would anyone happen to have a blank CD rewriteable or such sitting around?

ATTENDEE: Yes, we do. Of course.

[Pause.]

DR. CURLEY: Do you want me to start the movie, Paul?

COL PASQUINA: Yes.

[Pause.]

COL PASQUINA: If I could introduce myself, I am Paul Pasquina, the Chief of Orthopedics and Rehabilitation at Walter Reed and Bethesda.

Let's start the DVD.

[DVD presentation.]

COL PASQUINA: I guess we have a bunch of engineers in the room or mostly engineers. That was from Catholic University's School of Architecture to see what they could do to kind of help with the war effort.

It is one thing to say what the various disciplines can bring to the war effort and helping out service members. I also love this film because -- and I don't mean anything by this, but the patients that we take care of every day, they are not biomarkers. They are not images on radiographs or MRIs or DTIs or whatever. They are individuals with families, many of whom have gone to recently being married, playing high school sports, going out to the movies, and then all of a sudden, they are in an abnormal environment where people are trying to kill them. Their buddies are coming back losing parts of their body, and they are

trying to process all of that, at the same time where they might have had an injury themselves.

Particularly, it is very rare to find people that aren't exposed to some type of blast overseas with or without an alteration of consciousness, and I think that is how we define traumatic brain injury. It is some type of event that has some alteration of consciousness, but what does it mean for that person that has had not necessarily any clear alterations of consciousness, but has been exposed to multiple blast and then all of a sudden has problems with what we would traditionally call post-concussion syndrome, dizziness, poor memory, poor concentration, poor sleep, headaches, that type of symptom complex which is very, very similar to what people were reporting at Gulf War illness.

So there is this difficulty in managing patients with these symptoms. When we talk about TBI spectrum disorders, you are talking about some severe TBI folks that are in your ICUs that you are monitoring intracranial pressure, but you are also talking about this mild spectrum where people have a constellation of symptoms and have a lot of difficulty returning to their home environment or their communities.

Maybe we can just fly through this. I know we are over time. So I can talk through some slides, but certainly, I want to leave time.

I don't need to go over this. People are risking their lives every day overseas. IED explosions, we talked about that, but that is the weapon of choice of the enemy.

When we talk about blast injuries, people will talk about primary blast versus secondary blast. Has this already been talked about earlier today? If it has, I will just [inaudible].

ATTENDEE: [Inaudible.]

COL PASQUINA: So this idea that the primary blast wave, that causes problems to the brain, or is it the secondary effect of flying debris following that blast [inaudible], or is it that individual that is falling and hitting something or somebody falling on that individual, or the secondary medical problems, you know, anoxia, burns, metabolic problems that happen [inaudible] affect brain function?

We have medics saving lives, combat support hospital, and again, as was mentioned earlier, they are not just [inaudible]. They were evacuating pretty rapidly to Landstuhl [inaudible] Walter Reed, but when you think about that evacuation, it is pretty impressive that [inaudible], but then that secondary problem of now we are taking care of it at Walter Reed, [inaudible].

[COL Pasquina not speaking near microphone. Portions of his presentation were not transcribed.]

COL PASQUINA: Is my time up? Okay.

You know, rock climbing is something that -- you know, what we are looking to do for those with cognitive or traumatic brain injury problems is to incorporate physical rehabilitation strategies and throw in some cognitive stuff in there.

Theoretically -- and this is what we are working on now -- you can only use the red hand grips to climb a wall, or you can only use the yellow, or do you have signs that come up that are asking the memory questions as they are climbing the wall, so something that is going to challenge them physically as well as cognitively.

The KAREN [ph] system, we just had this put in [inaudible], as well as the one in Walter Reed, but this is an instrumented platform with a virtual reality environment. So, theoretically, you could work on cognitive skills. You could work on dialing in and dialing out, exposure therapy for folks with post traumatic stress disorder, as well as work on

things like balance and strength. So we need to all think about rehab techniques that will incorporate all of these things and getting them out on activities. It has been a huge plus, but how do we show benefit from that to where [inaudible].

Again, firearms simulation, returning to duty, social contacts, rehabilitation, and just to show you that technology does make a difference, it is pretty rare or it was pretty rare [inaudible], much less ambulate and carry their son on their soldier, to have that confidence in [inaudible], and their balance to be able to do something like that. So technology does have a huge role in the advancement of science, and [inaudible].

I think we will have time right the end.

DR. CURLEY: Yes.

COL PASQUINA: Sorry about the slide situation.

DR. CURLEY: Thank you, Paul.

[Applause.]

DR. CURLEY: Next, we have Dr. Nitish Thakor, Professor of Biomedical Engineering from Johns Hopkins University, and he is going to be discussing neuroprosthesis in rehabilitation.

[Pause.]

The Development of Neuroprosthetics in Rehabilitation

DR. THAKOR: Ken also in 15 minutes wanted me to add deep brain stimulation. I am not sure I can get to that, but I have slides. If there is time, I will do it.

Just at the outset, I want to say that anything presented here is a remarkable result of an incredible team assembled and thanks to tremendous government support. Time won't permit me to acknowledge everyone, but it is just really one of those magnificent projects I have been involved in.

Very quickly because of time, I will be going through many slides and movies and squeeze as much as I can.

As you know, the current state-of-the-art of prosthesis sort of ranges from something like this to [inaudible] to what is under development, and I want to quickly present what these things are.

Oh, the movies won't run. That is what I was afraid of. I have got a number of movies that are spectacular. Well, one of them is not working. So I don't know what to do.

I will move along, and if the other one doesn't work, then I will show you.

So tremendous prosthetic or robotics devices are under development at various places. However, one question is can we incorporate them in prosthetics work, so the development in robotics, how they impact prosthetics.

One other topic to consider is that traditionally, these prosthetics have been controlled by muscle signals from forearm or elsewhere, and how is that going to get revolutionized. For example, the ultimate way we can go do that is to use neurocontrol which could be both sensory, as well as motor, which means the brain can control.

The brain can control the prosthetic limb, as well as ideally it could capture the sensory information. So where are we on that part?

Forgive me. It looks like what I was afraid of. The movie is becoming a problem, and I am not sure what to do here.

[Pause.]

DR. THAKOR: Among the ways we can go about doing this in this amputee, transradial amputee, there are electrodes on the arm, and they are being used. If you see the

movie on this side, you will see the EMG signals being generated in real time, and then they can drive a virtual reality hand, which can then effectively -- this set of electrodes, information is being recorded to move individual fingers. So that gives us an idea that we can do that through muscle signals, or at least this is on the leading edge of what we are able to do now.

Now, moving forward is this spectacular work, again, out of the program that Geoff Ling leads, but Todd Tycan's [ph] work at Chicago where this individual, as you see, has been instrumented with a full arm, and it is being operated using a technique called muscle reinnovation, and I will tell you very briefly about that, but you can see he is a bilateral amputee, and what he can do is spectacular.

You saw this slide already, but it is also reaching the press where I think it makes a good job of public awareness of the need and what the technology can do.

So the program that Paul mentioned and Geoff Ling leads is creating a revolutionizing prosthetics program, which is to provide a full neurocontrol of 21 degrees of freedom arm, or at least that the long-term trajectory of that.

Just very quickly, it involves a number of institutions across the country and even outside, so a tremendous credit due to all those folks who made a lot of these things happen.

It has led to, as Paul mentioned, the DEKA arm, which is demonstrated here in this video, and this is an arm, an earlier version, that is being presented by Johns Hopkins Applied Physics Lab folks, and you can see that this latest generation arm is about to do multi-finger. It has multiple fingers, and it is able to actually address an individual finger. I will give you a little more update shortly. So you see the technology is moving forward really spectacularly.

What does it take to bring all of these together? It takes a lot of different things. Of course, this is the movie that you saw, but also the mechanisms that are being developed, there are a variety of hardware technologies that are under development here that pertain to mechanisms. Then there is a tremendous amount of control systems and electronics that go into it, [inaudible]. So we can talk about some of the Utah -- and other groups have developed micro electroarrays that can be used for implantation in the brain, and then at the current generation, we can test them in a virtual reality in our lab, as well as APL, and then those are the subjects who will benefit from it.

Here is one example of one subject who has benefitted and is undergoing some of the testing, and this is the slide as of October.

This is the gentleman you saw, Jesse, who with very limited training was able to do very dexterous tasks, as are depicted in these pictures. So I think these developments are very demonstrative of the progress that has been made.

Further development is going on in the arm that is looking more anthropomorphic as we go along, and again, you can see the multi-finger dexterous and shoulder, elbow, joints. These are all being implemented.

I am a biomedical engineer. So it is very pleasing for me. This young man is a biomedical engineer at Duke, and he is the one testing this early generation APL Johns Hopkins prosthetic arm.

So the next step is going to be neural integration, how do you put it all together. So it has many set elements to it. The critical one is implantation of these electrodes in the brain and then doing the signal processing and recording and all that and then actuating and controlling this arm. So I want to tell you briefly about that.

There has been in the last decade or so or the last few years, tremendous work in the ADL brain machine interface or brain computer interface using neural activity or EG activity to do certain tasks such as for a quadriplegic, they can move the cursor on a computer screen and so on.

So an example of a simple brain machine interface using noninvasive techniques, you will see here this young man is a student in our lab who wears an EG cap, and his EG signals, he thinks about the intent to move this hand. The simple EG wireless amplifier is controlling this multi-finger dexterous hand, and he is able to open and close it. So there are some signal processing algorithms that are needed to achieve this control. So you can do this noninvasively, but the degrees of freedom and capabilities are significantly limited to what we would like to do.

The next generation draws from a considerable basic research that is going on in various labs -- let me try to run the movie -- so that these are studies being done in primates, so that the electrodes are implanted in a primate brain, and the information is recorded. So that using a virtual arm or prosthetic arm or robotic arm, this primate can actually move his or her hand or arm and, for example, in this case feed itself.

So primate research has contributed to our goals of moving forward. You may ask the question will it ever go to humans. There is considerable progress at Brown University and Cyber Kinetics where implantable electrode arrays are being used to now control a cursor on a computer screen by the subject.

So we are laying down this trajectory on a step-by-step basis, including reaching a point where it now is ready for in some way, in this case, for human use under an investigational device exemption.

You can say where is the dexterity. So what is, in a sense, the grand challenge? For example, you can ask the question can we totally invoke the dexterity of a human hand, like, for example, can a monkey play a piano. I mean, it is a rhetorical question, but interesting. I will show you in some way how we can contrive that.

So what it is going to take is to put microelectrodes in the brain. This is some complex neural activity. We will have to decode it and then drive a dexterous robotic hand.

This is very quick neuroscience here. This is brain, and you look at little colorful dots. These are the places where information in the brain to code for individual finger exists. So it is a very hydrogenous mix. Each color code represents a particular finger movement, deflection, extension, size represents its activity level. So it is very complex. Our job is to decode that. So we use techniques like [inaudible] methods to identify which neurons are the ones that are active.

If you go into this monkey's brain, you find there are all these regions in a heterogenesis way where these crosses dots are is where the information, and that roughly about 4-millimeter cube is the information for finger movement is there. So we have to record that. By the way, these recordings, of course, done using microelectrodes in the brain, but this is a very recent result. If we are able to -- using that population of neurons, roughly about 30 neurons, record for position, velocity, and acceleration of individual fingers and also wrist rotation. So information exists in the brain. If you can put microelectrodes and using the signal processing methods that I just alluded to, you can record for individual finger, wrist, and hand movement.

So now the challenge is to put it all together. So I ask you the rhetorical question. Can a monkey play the piano? Well, this is a virtual animation of that. This is a monkey. It is being played back real time, but of course, really from a computer, and it is

being recorded and played back into this hand which then is in front of a piano. So it is not that the monkey knows how to play piano, but it is something we have contrived to do so. As I said, even something like 30 to 40 neurons, this is what the draft shows. We can do that kind of finger and hand recording. So it is very, very exciting.

So I think currently, as we can see where we are, it is that this prosthetic hand project has moved forward tremendously. This is an even later version where cosmetics is put on this hand, so that it almost looks like skin-like.

In this animation, you will see a further demonstration of this hand being used by John, and he is activating individual fingers. A lot of this is by recording muscle. So we really have to put the brain activity part that I showed you and the arm development, all of that, together.

As I said, it is an incredible effort, particularly led by the APL team, but a consortium of people who were involved in developing, underlying, engineering, and so on and so forth to bring us to this point.

Then finally, Stuart Oshbach [ph], who was the manager of this project, just gave me this video yesterday, and he told me that this subject in Europe was able to learn to use this arm within 30 minutes to an hour. So it wasn't like there was a tremendous straining required either.

So I would say it is really a prosthetic revolution that is underway, and you can see the tip of the ice berg in this work, and a lot of science and technology is coming to bear.

Now I have a question. I went very fast. Do you want me to cover DBS or not? Two minutes exactly.

ATTENDEE: [Inaudible.]

DR. THAKOR: So plenty of time.

The point is that I want to switch gears. Basically, deep rain stimulation, because it is potentially a powerful therapy for a variety of neurological disorders and since we led with a lot of today was about different neural injuries and impairments and therapeutics, I think deep brain stimulation must be considered downstream.

I am not necessarily alluding to traumatic brain injury, but what is out there, just to give you a flavor for what is out there.

I am about to do a very fast-paced sort of view of what deep brain simulation is. This animation basically already showed you what it is, some pacemaker-like devices implanted, deep wires, electrodes going to the deep nuclei of the brain. The basic idea is an electrode goes into the brain. If electrical stimulation is given, it produces and excites and stimulates these neurons.

When you do that, remarkable things happen. This patient has Parkinson's disease in his arm. If the stimulator is on, it looks very normal. When the stimulator isn't on, you will see the Parkinsonian tremor and instable [inaudible] take over, or other things that can correct is this handwriting, which is very indicative of Parkinsonianism, and again, stimulation can fix, find, as well as gross motor movement. So this is success.

Now already there are about 2,000 people with these kind of implants, but moving forward, not only Parkinson's, but essential tremor or dystonia. In this case, this young lady I think will show that stimulation will make an effect, and while you look at it, there are a number of other ideas that are under development which are not FDA approved. So most stimulation, you can see how much remarkable a difference it has made.

So moving forward, what is going on in all of these various disorders -- and these are all non-FDA approved and experimental or investigational projects. So looking again, I will just give you a panorama of things that have been published. Implant boost activity in injured brain, so for consciousness, this was published in Nature in August of last year. This one is a study that talks about depression where deep brain stimulation may be used for treatment-resistant depression. Obsessive compulsive disorder, so that some outcome studies that demonstrate this is applicable that. Tourette syndrome, again, GP global [inaudible] nuclei that are stimulated may affect, improve the ticks that might be seen in Tourette syndrome.

Medtronic is either finishing off or reporting this study that is deep brain stimulation for epilepsy. This company, [inaudible] is looking at electrocortical, sort of subdural electrode arrays for stimulation for [inaudible]. There is research on control of pain, and then perhaps going forward, memory enhancement. It is not for us just yet, but I imagine drug companies and other companies might be interested or my kids might be interested for their exams and so on.

My part is this is sort of like a Wild West right now. So I brought up this slide. There is so much going on, but science lags back tremendously. It is very empirical. There is some technology for all of that, but the scientific foundation on most of these disorders and therapies is quite unknown. So that is why I treat it as a Wild West, just go around as fast as we can and find all these therapies, and then we will see what works out.

So, just in closing, I think my 15 minutes previous is just that I really think we have to be incredibly optimistic. This is the time for the brain. Whether it is neural interface, stimulation, or prosthesis, it is just that revolutionary things and spectacular things are happening through our collective effort. So I think that is it.

I very quickly want to thank a lot of people and thank you all for your time, all in 15 minutes.

[Applause.]

DR. THAKOR: If you have any questions or maybe later.

DR. CURLEY: Thank you very much.

Next, we have Dr. Smita Svant-Bhonsale, Vice President and General Manager of Theradigm, and Smita is going to be talking about regenerative medicine in the CNS. These two thoughts, [inaudible].

ATTENDEES: [Inaudible.]

Tissue Engineering and Regenerative Medicine CNS as an Approach to Rehabilitation

DR. SAVANT-BHONSALE: I would like to thank Dr. Curley to invite us, so that we can share our exciting data with you.

The thing is I am not an engineer. So I am going to change a gear a lot, and hopefully, I won't lose my audience and keep you guys engaged and interested in our work.

We are basically a local company. We are in Baltimore, Maryland, and we are working to develop stem cell therapy for a number of brain or spinal cord injuries.

Currently, we are focusing on traumatic brain injury and stroke for the brain and then spinal cord injury and ALS for spinal cord trauma.

When I say stem cells, a lot of things go in people's mind because it is election year, and a lot of talk is going on about stem cells. The type of cells we use are all [inaudible] stem cells. They are either derived from bone marrow or neural stem cells, which

are derived from the fetal brains, or adipose tissues specifically derived from the liposuction, you know, the fat you get. We get cells from those, or umbilical cord [inaudible] stem cells.

Today's talk, I am going to focus just on the first type of stem cells because that is where we have the most data.

As a company, we had to have a technological advantage as well as commercial advantage because the goal of our company is to bring this therapy to clinic. So the advantages of our cell types are that they [inaudible] express number of trophic factors such as trophic factors which promote angiogenesis. That is making new blood vessels, promotes endogenous stem cells. It also [inaudible] tissues, and it facilities complexity modeling of brain and spinal cord. I hope to show some data today because, as Dr. Curley said, it is only 15 minutes, and I have to hurry through my slides.

[Inaudible] historically has shown safety because, if you recall, bone marrow transplantation has been going on for last 35 years very successfully, and this is unrelated bone marrow transplantation I am talking about, and we do get these cells from bone marrows.

We have shown efficacy in the animal models for a number of CNS injuries; for example, as I said, TBI, stroke, MS, and [inaudible] hemorrhage.

These cells have another advantage over, for example, embryonic stem cells or other cell types I talked to you about. These cells are immunosuppressive. They don't cause any immune response when we inject these cells. So that we don't have to give any immunosuppressants to the patients when we are treating them.

The mechanism and therapeutic window of efficacy is suitable for acute and subacute applications like, for example, in theater or whatever, that can we get to the patient in time, because, for example, some of you know that for the stroke, the treatment is TPN. You have to administer that very shortly after the stroke. If you don't do that, then it is not very efficacious. So we needed to come up with a therapeutic window which allows us to treat the patient even in a suitable manner.

So there are several commercial advantages to this that our formulation is going to be basically cryopreserved or frozen cells, you know. So we can support battlefield applications.

They are very well characterized, easy to source, grow, freeze, and store and delivery. Then they are very easy to administer, also. I will show you some data that we have looked at the different routes of administration into the animal models, and we found that even IV administration works pretty well.

They do migrate to site of injury and across the [inaudible] barrier. I already told you that because they are non-immunogenic, we can develop a product which is off the shelf, so that we can get source from a donor, grow them in large quantities, and then cyropreserve them, freeze them, so as per need we can ship them to the site.

They are safe in animal models. We have so far not seen any tumors or any kind of adverse effects, and when I say animal models, I am talking about thousands and thousands of animals we have done for different indications with our collaborators, and I think I covered these.

So today, I am going to talk about TBI first, stroke a little bit, and then very little for spinal cord injury because that is the order we have most data on.

For this audience, I didn't need to show this, but not knowing my audience very well, I apologize for having this slide, but we all know that in civilian world, the major

cause of long- and short-term disability in young adults is traumatic brain injury, and it is much, much higher in military personnel.

So, as Dr. Pasquina showed us the film, it shows that there is a very large unmet medical need to come up with some sort of a treatment, either [inaudible] medicine or prosthetics or diagnostic. In many ways, there is a lot to be learned and a lot to be developed.

So, as I said, we tried to inject these cells in different ways in the rat animal model for traumatic brain injury directly into the brain or into the carotid artery or even in [inaudible]. So today's data, I mostly will talk about what is in these [inaudible] elsewhere delivered in the [inaudible] because, again, we wanted to develop a therapy where we can deliver this elsewhere easily in the field, you know. The patient already has a trauma. You don't want to drill a hole in the skull again. So, if you could do it through IV, it is a lot easier to develop and deliver.

So once we inject the cells, we want to see where they go and what do they become because that is very critical. These are not chemicals which will get destroyed. These are live things. So you want to make sure they don't migrate to wrong site or they don't cause any more problems than already there are associated with the injury.

So what we did here was we injected the human bone marrow-derived stem cell into a rat animal model, and that way, we can identify our cells because the human nuclei has a specific protein that they express which we can detect with an antibody which recognizes only human nuclear protein. So that way, we can show that these cells do migrate to the site of injury, and here, I am showing you the lesion boundary zone. All these bright blue dots are the nuclei of rat brain while these pink dots are the nuclei of human nuclei. So that means these cells, even though we injected them in the tail, they travel all the way to the brain or sited next to the lesion.

This phenomenon we see which is quite dose-dependent, we try 2 million cells per animal, 4 million cells per animal, 8 million cells per animal, and we counted how many cells we can see per millimeter square of a brain section, and as you can see, the more we inject, obviously more cells end up there.

The other thing I alluded to you, the way these cells help regenerate or repair or help regenerate the damaged tissue is by providing growth factors, and these are some examples of growth factors. These cells express in vitro, as well as in vivo. In this brain section, as you can see, they are expressing number of factors which are known to form the neurons or new synopsis. So that is the good news that they can express NGF and BDNF.

Basic LGF is known to require for the neural stem cell proliferation. So that gives us the mechanism that maybe these cells express basic LGF and help the endogenous stem cells proliferate or make more of the endogenous stem cells, and that should help regenerate the damaged tissue.

BGF is the factor which is known to be angiogenic factor, so that it can make new blood vessels, and that comes in the role when you have a stroke.

We also looked at -- here I am just giving you an example of one of the factors that we [inaudible], and we saw that in the control when we don't inject any cells and just give PBS or saline, where it says when you inject either 2 million, 4 million, or 8 million cells in a rat which has traumatic brain injury, and as you can see that again, the dose dependent did increase in the BDNF expression into the injured animal brain, and black boxes are the [inaudible] hemisphere, while the open boxes are the [inaudible]. That is where the damage was done, and as I said, these cells like to gravitate towards the site of injury, and that is why we are seeing more BDNF expression in the injury site.

We also looked at the efficacy of these cells, and by that, we looked at sensory, motor, and reflex skills of these animals before and after the treatment. Again, there is not a significant difference between the different dose levels between 4 million, 8 million, and 2 million cells. We didn't see much significance.

Now, here the way we scored these animals is one point is awarded for inability to correctly perform a task or a lack reflects that we are checking. So there is a battery of tests we do to test their sensory, motor, and reflex skills, and then this data is just a tabulation of all that. So lower the score, better the recovery.

The other thing we looked at is combination therapy, that in combination with cells, can we improve on these cells to perform better, and one of the things we looked at was using [inaudible]. So these cells are more localized or we can transplant them very near the site of injury, and here the example is with the [inaudible] implanted intracranially into the TBI rats, and again, you can see that when we adjusted BMSC, the [inaudible] was reduced, but not as significantly as when we do the [inaudible] embedded with our BMSCs.

Again, this correlates quite well with the lesion volume, you know, that when we have BMSC injected, we get smaller lesion while compared to the saline, but adding the [inaudible] to our treatment makes the volume even smaller.

This is another just task that we did after treating the rats with our BMSCs for one month. This is called the water maze analysis where you basically let the rat -- it is a pool of water. You put the rat in there, and then basically ask the rat to find the platform where it can climb, and the platform stays in the same quadrant all the time, but you put rat in a different quadrant. So the amount of time the rat takes to swim around to find the platform is recorded, and then again, you can see that we saw the best recovery of efficacy when we had a [inaudible] and BMSC as a treatment.

So, to summarize just this program, the Traumatic Brain Injury program, all the data I showed you was all preclinical data performed in Dr. Aseen Mamood's [ph] lab in Henry Ford Hospital, and as I said, we showed that these human BMSCs are even efficacy in the rat TBM model, and then we are collaborating with Dr. Frank Tortella at Walter Reed Army Institute of Research to show the same or similar studies, efficacious studies, to show that it also works in another type of traumatic brain injury model, which is more related to the combat injury. Hopefully, next time when we talk, I can give you the update on that data.

Preclinical studies for dosing and therapeutic windows are underway for both TBI and the CCI model. The first model I showed you is more like a contusion an injury rather than the ballistic injury.

We are planning to have an IND meeting, pre-IND meeting with FDA to propose BMSCs are a therapy for traumatic brain injury patients with allogenic BMSCs and also preclinical studies for combination therapy with BMSCs in [inaudible] and BMSCs with statins, short efficacy, and we are doing more work to prove the efficacy and get more data.

The second program I am going to talk to you about quickly is stroke. Again, here, quickly, there is efficacy with the BMSCs because we see improved neurological function, and here, you can see that this is a very impressive slide. This is with stroke. You don't see blood vessels are lost due to the ischemic injury. While treatment of BSMCs, you can see lot more blood vessels generated.

The other problem with stroke is you get [inaudible] scar, and BMSCs, you get reduction of that. Also, we see white matter bundles in striatums. They also get improved with BMSCs. Even in the spinal cord, you see regeneration when we treat stroke animals with human BMSCs.

So this is our stroke program, preclinical studies, and again, we already had a pre-IND meeting with FDA, and we are just finishing our last pivotal study, safety study, so that we can find for IND to treat stroke patients.

I couldn't miss this because Dr. Curley is quite interested in this program, and this is our Spinal Cord Injury program. As I said, we have the last amount of data, but here also, this is actually models, animal model. We create a spinal cord injury, and then here the cells we used are a little different cells. These are fetal spinal cord-derived stem cells, and we are showing that they fill up the cavities. So these blue dots you are seeing are cells. The black arrow is where the injury was, and the red arrow is where the cells were transplanted. As you can see, they are filling up the cavity very nicely, but in this case, when we used the immunosuppressants, actually the cells started migrating away from the cavity, and we don't know why.

So instead of filling up the cavity, they kind of migrated all the way, almost 8.5 millimeters away from the cavity, and then when we did [inaudible] injections to the center of cavity, we saw some migration, and here, you can see there are number of cells which survived in the injured environment, and we haven't done any efficacy data on that.

But quickly, these are all our beautiful cells, and here some of them, the different aspect of these cells are they do differentiate into the neuronal cell types. For example, these transplanted cells differentiated into astrocytes, which are one of the CNS cell types, and then also we saw some differentiation of these NSPCs into all [inaudible]. That is another cell type, and we saw some neuronal differentiation also, but I don't have time to show you that data.

So the spinal cord injury program is kind of new. We don't have as much data, but we are working with University of Miami to finish these studies, and we have applied for more funding from Maryland Stem Cell Fund.

I must thank [inaudible] Capital for funding our company, and then TBI studies were done in Dr. Mamood's lab in Henry Ford Hospital. Stroke studies were done in Dr. Chop's [ph] lab in Henry Ford Hospital, while the spinal cord injury studies were done in Damien Pierce's [ph] lab at University of Miami.

I thank you very much for staying with me.

[Applause.]

DR. CURLEY: Thank you. Thank you, Smita.

Just to correct something I had said earlier, I said minimally conscious state, the deep brain stimulation was subthalamic nucleus, and it was actually thalamus. The stimulator was placed in the thalamus of that patient.

Next, I would like to invite Jacob Rosen up. Dr. Rosen is from the University of Washington, Research Associate Professor, and he is going to discuss the use of robotics for physical rehabilitation.

Use of Robotics for Physical Rehabilitation

DR. ROSEN: Okay. So, rather than being selfish, I will give you an overview of the field and in general, and these are just things that I do.

So, in terms of assisting robotics, there are actually two classes. One is a manipulation, and there are two things you can do with it. The first thing is you can rehabilitate with it. So that is the term which you can power-fit, and the other one is you can use it as a way to interact with the world around us. If you are a disabled person, obviously this is what you want.

The second class is then mobility, and these are different systems that can provide you some locomotion.

So what are the premises? In terms of therapeutic, we want to keep the therapists in the loop. So they feel that robotics will take them out of the process, but that is not the intention, and in terms of the patient, we want to retrain the neuromuscular system following an injury.

We are taking advantage of the plasticity of the brain and the redundancy of the human body, and I will talk about that later.

So what the robot can do for you, it can maximize the neuromuscular recovery, and it can do multiple functions. It can be used for therapy, for manipulation, and for locomotion.

So, if you ask why robotics, this is why. We want to eliminate scenarios like that where three peoples are trying to regenerate a projectory off a patient.

To give you an overview of how funding is flowing into our system, this is a quick analysis of medline. We have [inaudible], and you can see how many publications were shown up. This hairline is a presentation of what is robotics, rehabilitation robotics as compared to rehabilitation in general.

An interesting comparison is to show what is rehabilitation robotics with respect to the whole robotics field. So it is about 5 percent.

Another interesting way to look at this is what are the injuries that robotics is targeting, and the majority are stroke.

Other interesting ways to look at how many publications were published, how many manuscripts were published, you see it is a function of -- in the past 10 years, you see an exponential growth in rehabilitation robotics.

So what are the pros? The first thing is high throughput. You want to [inaudible] from the scenario where you have one-on-one therapy. You can have several stations where the therapists can treat multiple patients simultaneously.

There are different modes of operation. You can compensate for gravity. You can assist with [inaudible], create force control and narrow control, and the most important thing is you can provide quantitative information.

Right now when you ask a therapist what do you do, they will tell you, "Well, I look at the patient, and I sort of create some therapeutic regime, and I follow that," but obviously, that is not a scientific way to treat these things.

The only disadvantage is that we lose the human touch.

So I will just breeze through several systems developed in academic, and before we get to that, I just want to give you some intuition regarding manipulation.

So I have this object in space, and I want to position and orient that object. I need six parameters, so the XYZ of that object and the three rotations of that object.

Our arm has seven degrees of freedom. So the fact that I can put this object in space and I can still move my elbow, that is a redundancy that I have in my arm, and I am excluding [inaudible] movement. So any system that doesn't support our seven degrees of freedom of our arm is somehow limited in its ability to rehabilitate.

So, in all the systems that I will show, keep that in mind. I think I listed the degrees of freedom in each one.

So, in the early '90s, people used industrial robots that essentially can kill you if you are not careful, and they used them for rehabilitation. So they put the patient, attached

it to the under effect, and here the patient can move with the healthy side and create [inaudible] image and move the other one.

This is a famous machine from MIT. Yet again, it is limited to a single plane. So it is two-dimensional instead of three-dimensional.

Another two-dimensional system, another one which is based on commercial arm that is attached to the human arm for a custom-made interface.

This is a full arm [inaudible], and you will see that later on. It is supporting four out of the seven degrees of freedom that we have in our arm.

This is another one, again, compensating for gravity in a plane manipulation.

Recently, U of Maryland and Georgetown developed this [inaudible]. It has five degrees of freedom. Again, it is missing the tool that we need to fully manipulate our arm.

Another one from Panasonic, and for low limb, you have systems like that. It is [inaudible] that actually can flex and extend your leg, and a more comprehensive one by a company called Ocroma [ph], and it can take a patient for the entire gait cycle, using all the degrees of freedom that we have in our legs.

There are other systems that were sort of developed through the [inaudible] support, but they were not necessarily dedicated to rehabilitation. So I just mention them over here.

So I was personally involved in developing several generations of [inaudible], and you can see one degree of freedom of just the elbow and three degrees of freedom of the shoulder and the elbow, and most recently, this device which is a seven degrees of freedom [inaudible], and you look here on the side of [inaudible], and you gain a lot of appreciation to the strength of our muscles and the strength to size when you try to create it with DC models. So I think we are quite impressive in that respect.

So we built two arms like that, and I will show you some preliminary experiments with these arms. So I don't know how to play that.

To show you the various degrees of freedom you have three degrees of freedom for the shoulder and upper arm rotation and elbow flexion and extension, forearm rotation, and two degrees of freedom at the waist. So, essentially, this arm would follow any point in space, and you can even scratch your back with it.

So one of the preliminary experiments that we have done, we wanted to look at the human arm [inaudible] and dynamics. So what you typically do, you put a subject in a motion capturing [inaudible], and you ask the subject to perform different daily activities. So you recalled all the [inaudible] and dynamics of the human arm in space.

If I play back this clip, you will see a [inaudible] movement. What you can see is how graceful is the way we move our arm. We are still struggling with the idea of how to solve the inverse schematics of the human arm, and the problem is that as I said, we have six degrees of freedom of manipulating an object, and we have seven degrees of freedom in our arm. So we have an extra degree of freedom. So serving the inverse schematics of redundant manipulation is you need to add an extra equation, and this is the equation that the brain is actually adding as you manipulate the object. So what is the criteria the brain is using to do that, we still don't know.

What I wanted to show here, these are the equation of motion of the human arm, and so these are the [inaudible], and the [inaudible] is a function of the inertia [inaudible] and gravity. So you see there are seven equations, seven [inaudible] or seven joints, and on the right-hand side is something we can measure.

The question is what is the contribution for each one of these elements to the joint. So this is an experimental result of which movements. So you see position on the top, velocity, joint velocity, joint acceleration, and eventually the joint [inaudible] in blue is the overall [inaudible]. In black, you will see the gravitational component, and in pink, you will see the inertial and velocity component.

What this graph will tell you is the major component in the [inaudible] is gravity, meaning that when I do this movement, I manually fight gravity, and I don't really devote too much [inaudible] to actually manipulate the object, and the implication for rehabilitation is that when you try to assist a disabled person to recover, you really need to support the gravity of its own arm, and you can gradually decrease the gravity as the rehabilitation process would proceed, but that is probably the limiting factor in human arm manipulation.

Another experiment that I want to show you is we use this device for muscle amplification. So you have a load, and you have the human and [inaudible]. You want the human to carry a small fraction of the load. So there are different ways to position the interface. We decided to pick [inaudible] interface. In our case, it is an EMG signal, and this is our window of opportunity.

So there is an existing time delay in our system between the time you can pick the signal and the time that the skeletal muscle would move, and during this time delay, all the [inaudible] actually involved in contracting the muscle. So we have a window of opportunity to predict what the muscle will do before the muscle will actually move.

The elements that would do it, it is called the [inaudible] take neural signals, joint angle and joint velocity and predict for us the joint talk. So a crash course in muscle physiology, the muscle is generating force as a function of its length and a function of its velocity. So you can generate an envelope like that, and at any point on this envelope is an operational point in the muscle.

Experimental results, this is a flection and distension of the elbow with an assistant of the [inaudible] and without. So, without an assistant, you see very high neural activity, and with an assistant, you can see how the neural activity significantly dropped.

These are the joint talks of the load and the joint talks of operators, so when you don't assist, they are similar. When you assist, you see the load would be still the same, and this is what the human would have to do. So the difference is what the [inaudible] would do for you.

Just to summarize, this is a result of about 200 experiments. Each point is an experiment here. You can see the white is a representation of an unstable operation, and what you can see here is a map of different inputs and signals, and neural input and forced feedback input. So, if you don't use any neural signal, the gain that you can get is about eight, but once you introduce a neural input, then you can almost double the gain, meaning that 16 is you feel one of the 16 of the external load.

So conclusion, funding. There is no further agency that claim the fame for rehabilitation robotics. So it is sort of falling between many agencies.

The robotic device itself would still be challenging because, first, there are very few groups that know how to design this complex mechanism, and really doesn't really help because it almost doesn't exist.

Economy, cost, benefit, it is another issue. A system like that is equivalent to an annual salary of a physical therapist. Using this same information, you should convince a

hospital to buy something like that. It will start return the investment probably after a year, but that is challenging.

Occupational therapy, the communities will need to accept that. We want to move the therapies from the physical manipulation of bodies to a decision-maker, and that is probably more appropriate for a therapist to be.

An accomplishment, several studies show that we can accelerate and get better end results mainly in stroke and because this is a field that was extensively studies.

A few demonstration of [inaudible] over the web were made. Open research question, we don't know what is the algorithm to rehabilitation people. We don't know what is the optimal dose to do that. Should we intervene in the early stage where the system is unstable, or should we wait when the system will be stable?

We don't have objective measure to assess disability, and the vision is we want to introduce an intelligent layer that would sort of monitor the treatment and keep the human out of the loop.

Thank you.

[Applause.]

DR. CURLEY: I would like to invite Dr. Scott Frey up. He is Director of the Lewis Center for Neuroimaging at the University of Oregon.

Use of fMRI to Assess Brain Function
During Rehabilitation

DR. FREY: Well, I had to come all the way from Oregon just to get some snow. Every time I am here, it is snowing. It is very unusual. It doesn't jibe with my memories of Washington at all.

I wanted to thank Dr. Curley and Dr. Pasquina for inviting me all the way from Oregon to come here and talk to you a little bit about my work.

Fortunately or unfortunately, I don't have any conflicts to declare, although my kids would probably be happier when it comes to college if I did.

My title may seem rather broad, and it is. Lumping together brain and bodily injury in 15 minutes is an enormous task, but let me just tell you a little bit why I have chosen to discuss these two larger sets of problems in one slide, and the reason is really pretty simple

We know that when you have an injury to your body, such as an amputation, that that actually does cause changes in healthy brains. So, even without a traumatic brain injury, if you lose a hand, if you lose a foot, we can through the use of noninvasive methods actually visualize some of the changes that are taking place in terms of the areas that were previously devoted to that now-amputated limb, and we think that some of those sorts of reorganizational changes in healthy brain might actually have behavioral components and experiential components that may interfere with rehab, such as phantom limb pain, and that might a better understanding of them might also help us to be more sensitive in designing more efficacious rehab treatments.

The work in my laboratory is focused pretty heavily on using noninvasive neuroimaging techniques, most notably blood oxygen level-dependent functional MRI, which is the sort of standard way that most people do functional magnetic resonance imaging when you look at physiology in individuals who have had focal strokes and in individuals who have had bodily injuries and most notably amputations of the upper extremities.

This is probably the wrong point to make this division because all of you have been sitting through talks, many of which involved imaging today. We can sort of broadly

talk about neuroimaging in terms of structural imaging, and you see an example here where we have got some high-resolution anatomical image up top with some tracts that we have been able to mathematically describe in the white matter of the brain using diffusion tensor imaging and probablistic tractography, and on the other hand, we have got functional ways of looking at the physiology of the brain, which we can also do noninvasively.

I am going to focus exclusively today on functional neuroimaging. I am going to focus on using changes in the hemodynamics of the brain to make inferences about activity increases and decreases in the cerebral cortex in particular, although we can look at other subcortical structures as well. My focus today will be on the cerebral cortex, and I think a few selling points of using blood/oxygen level-dependent fMRI are that it is noninvasive, that it is quantitative, that we can look at measures in this signal over time, and that it involves no ionizing radiation. So it is nice and repeatable, unlike PET, for example.

It gives us pretty high spatial and moderate temporal resolution. We can use some clever tricks in terms of how we design our experiments and how we do signal processing to get some pretty reasonable temporal information of the time courses of activity in areas. It allows us to cover the entire brain. So we know that most of the kind of cognitive processes that we are interested in and even things that might for brain seem simple, but really aren't, like moving your arm, moving your finger, these involve complex distributed networks of cortical and subcortical structures, and functional MRI allows us to really visualize those entire networks.

We think that is really important, and to the limits of our own creative abilities as scientists, we can device novel and kind of creative ways of probing these physiological responses in trying to figure out what computational functions are implemented in these networks and what is going on, and depending on how we design our experiments, it is also possible to look at individual differences which, of course, when you are dealing with real people in a rehab setting, that is a nontrivial factor in terms of thinking about designing and implementing rehab strategies, monitoring them, and so forth.

Some of the applications of functional MRI, well, you can use it for surgical planning. You can map, for example, eloquent tissue and help to give your neurosurgeon some ideas of where they should be trying to not excise tissue from when resecting a tumor or focus is epilepsy.

You can look at outcomes. So you can follow a patient over time and see how the physiology of the brain is changing as they are undergoing a rehabilitative intervention.

What I am going to focus on are really two other ways that might seem a little bit less obvious, what I am going to call interventional fMRI. That is really using fMRI or looking at these brain responses in relation to experiential factors that we are manipulating to try and devise novel rehabilitation strategies; in other words, letting the neural responses to various kinds of tasks we are providing people with help us to fine-tune and optimize rehabilitative interventions, to target particular brain networks, but also to customize these interventions for different individuals as well.

I will say just a word or two about prognostics and the potential to use the fMRI signal to really tell us how far down the road recovery is likely to proceed in the future, and that is actually providing to be increasingly promising in the world of stroke, but we think it also may have broader applicability.

So these are just some of the kinds of things we can do with bold responses. We can visualize them and look at them in a variety of different ways and achieve reasonably high resolutions.

To illustrate interventional sorts of ways that the bold signal scan be used, I am going to use an example from my lab where we have been looking into mirror therapy. Some of you may or may not know about this idea that you can take an amputee, for example, an unilateral amputee -- and in my work, we work primarily in upper extremities, but we are starting to move to lower extremities. You can have them make a movement in front of a bilateral mirror, and you see a bilateral mirror positioned on the lap of a healthy control subject here.

You can imagine that on this side of this mirror that is on the left, the left hand is being reflected up to this mirror here. Then we can take a film of this mirror, and if we ask this information to move that left hand, but we have is an illusion really that movements, unilateral movements of that left hand are really bilateral movements. So you can imagine with a unilateral amputee, you can play this game, and you can provide this kind of false simulated bimanual feedback, even though they are just moving one limb.

There are a number of studies in the literature suggesting that that experience over time may actually have some efficacy in intervening with phantom limb pain, perhaps by stimulating reorganization in sensory motor areas of the brain, but we don't really know that because we haven't really looked at how the brain responds to this kind of circumstance, and this is something that we have been doing in my group.

So this is just zooming in on the sort of image that we can create of the reflected hand. So you imagine that in actuality, the subject is just moving one hand, it is going to look like two hands moving in unison. We can pipe that in through an image system and provide that kind of experience to the person while we are actively monitoring brain function.

What we can do is look at what sorts of factors and variables actually influence responses within areas of the brain that we think might be engaged by this kind of feedback.

We know that in your parietal cortices back here in the brain, there are areas that have multisensory representations of your body. That is, they are not just responsive to somatic sensory touch kind of stimulation of [inaudible] feedback, but they are also bringing together maps of the visual features, spatial characteristics of the body, and we think they are pretty good candidate areas for being stimulated by this kind of visual sensory feedback.

We have done a bunch of control experiments now to figure out how best to structure these kinds of task, is it important that when the person is moving one hand that the other hand -- in terms of control subjects, is it important what the other hand is doing, what they are thinking about the other hand doing and so forth, and what you are seeing here is some recent work that is still in the pilot stages.

We are running additional participants now in this trial, but what you are looking at are responses in unilateral amputees, and you are seeing some axial sections through the brain here. What you are seeing in color are those areas that are showing increased responses.

When we go from a situation where they are just seeing their one hand in this case being stimulated, we are just moving a brush over the one hand that they do have, seeing it like this with the mirror covered, versus a situation where we uncover the mirror and now it looks as though we are applying stimulation not only to the hand they have, but the hand that they don't have. So they are seeing and at the same time they are feeling on the one hand, but they are seeing it as though it is happening on both hands. In that circumstance, we get a nice up regulation of activity when that mirror image is revealed in posterior parietal cortex,

in these areas that we think about as having this kind of multisensory integrative function in terms of the representation of the body.

We can do the same trick but ask the patient to be more actively engaged; that is, we can ask them to make a movement with the unilateral hand that they do have, and we can at the same time play this game of covering and uncovering the mirror.

What was interesting to us in our experiments with healthy controls is that just having them watch the hand moving and seeing its reflection in the mirror didn't seem to give us much bang for the buck at all. It was only when we asked them to watch the hand moving and its reflection and imagine that the hand that they are holding still behind that mirror is going along with hit. It is only when we tapped into this ability that we have to mentally assimilate movements in our head, motor imagery which is something my group and others have worked on a lot with respect to changes in brain activity that may have or may not have rehabilitation potential. It is only when we combined motor imagery with the mirror feedback, kind of giving visual sensory experiences as though both hands are moving in these unilateral amputees that we see these kinds of responses, again, very strong bilateral responses in areas of the brain that this condition with the mirror uncovered relative to the mirror covered when they are making movements as well.

So the obvious next step for us and one that we are beginning now, we know something about how the brain responds and controls. We know something about how the brain is responding in these unilateral amputees, and interestingly enough, it is activating these responses bilaterally, even though they have been without a hand for some period of time, quite variable, and we would like to see whether this has any therapeutic efficacy, does driving these kind of polysensory areas of the brain actually have any kind of utility in terms of intervening, particularly with the phantom limb pain that they have, and we also have some early pilot work ongoing with chronic hemiparetic stroke patients.

So I think my point in showing this to you was the idea that we can do experiments with functional MRI, and we can let the response of the brain tell us about what factors, what manipulations in that environment actually are driving neural responses, and for example, in our control work, we found that unless people were actively imagining movements of that limb, we probably weren't going to be able to engage these areas very effectively. We wouldn't have known that without having done these kinds of functional imaging studies.

So we like to think of this role as an interventional role for this kind of fundamental brain and helping to give us sort of neurally inspired sorts of methodologies, and I think the next level to take it is to think about how we might be able to tailor this to the inherent individual differences we see across patients as well.

The final thing I want to tell you about is just the prognostic sort of potential of functional MRI. This is some data that looks really strange because we have displayed it on a cortical surface that has been unfolded, so we can see down in the sulci and the figures of the brain better up here, and then we have also flat-mapped the cortex here. So we have kind of unfolded it and flattened it, which allows us to start to look even in greater detail about the loci of these activations and their spatial extent and so on.

This is a unilateral allogenic hand transplant patient. One of the things that we have been doing lately on collaboration with our colleagues at the University of Louisville is looking at changes in sensory and motor areas of the brain as allogenic hand transplant patients, and this is our first patient here, our recovery use of this new hand.

This gentleman is particularly interesting to us because from the perspective of neuroscience, he should be profoundly reorganized in terms of sensory and motor cortices. He was without his right hand for 35 years. He has got a new hand. As a neuroscientist, I would have said that is a terrible candidate for the surgery, and I think I would have been wrong because his functional outcome is quite remarkable.

So we are looking over time at the sorts of changes in his brain, and one of the things that we are seeing is that some of the changes that we are seeing in motor areas of the brain and in sensory areas in response to stimulation of that hand actually are preceding his return of function behaviorally. We think that this may provide some opportunity to evaluate the prognostic possibilities of this technique.

So can we predict from signals, earlier recorded signals of sensory maps in the hand, even when he has extremely limited sensory function, future potential for sensory gain, and that is a question that is open and one that we are looking at now as we bring him back repeatedly over time.

So what is the future for this? Well, I think the future is bright, and I think that just to kind of hit on a couple highlights that I have already mentioned, I think functional MRI has real potential for helping us to come up with novel sorts of rehabilitation protocols that are guided by the responses of the brain to really figure out what the critical variables might be in those protocols; in other words, to help design these rehabilitation tasks in a way that really optimizes them to target the particular neural networks and structures we are interested in.

I also think it is important -- and I think this came up in Dr. Pasquina's presentation -- to point out the fact that each of these patients, though they may have an amputation, let's say, of a left arm below the elbow, each of them is individual, and if you are a neuroscientist and you are doing this kind if in vivo imaging, you would know that the responses in the brain have a lot of commonalities, but there are a lot of interesting individual variations as well. I think it is really important, and that one of the potentials that this kind of imaging technique has is to really help us to refine techniques and perhaps in the future be able to customize them to the individual.

Then of course, there is the issue of looking at the response of the whole brain and trying to figure out how that might help us to develop better systems and prosthetic technologies and brain-controlled interfaces and so forth.

I just want to say thanks to the different agencies, including TATRC who has been supportive of the variety of projects that are ongoing in my life.

[Applause.]

Panel Discussion III: Policy Changes

DR. CURLEY: I would like to start the panelist session. We will start with Dr. Myklebust. Joe Myklebust is Director of Division of Physics, Food and Drug Administration.

DR. MYKLEBUST: I don't have a PowerPoint presentation. When I thought about what I could do here, I realized that any presentation that I make would need to be cleared, and the cleared presentation, if I had my presentation cleared, I would probably be up here explaining to you what an IDE is and what a 510(k) is and what PMA is, and even though I only have 5 minutes, I am pretty sure that I could put the entire room out with no problem.

What I wanted to do was to just make a couple of observations based a little bit on some of my experience and some of the presentations that we have heard today.

I wanted to say, first of all, that I am really pleased to be here. I think this is an example of something that AIMBE can do, a great model for AIMBE in a number of different programmatic areas that I think would be really, really valuable. So I think this is really a great event, thanks to TATRC.

Although I am at the FDA now, my more recent past before that was with an agency called the National Institute on Disability and Rehabilitation Research which maintains a significant portfolio of research in spinal cord injury, TBI, these kinds of things, and one of the things I remember from my time there, I spent a lot of time on interagency committees and so forth. There is one in particular that I went to regularly on some aspects of medical rehabilitation, and we could count on one of the people from another one of our sister agencies that was responsible for funding care in these areas to at every meeting get up and in a very impressive tone of voice say, "Of course, you know there is no evidence that any of these treatments work in traumatic brain injury."

Now, what she meant was, of course, there is no large-scale, multi-center clinical trial that supports the particular therapies we were talking about, and putting aside whether or not that is really the best way to make that judgment, that is another debate.

After thinking about this, the realization that you come to is that the reason for that is the heterogeneity in traumatic brain injury. We heard that referred to a bit earlier this morning. The comment was made that we can see people who have very similar injuries, apparently similar injuries, who have significantly different outcomes. So I think that one of the conclusions that I have been coming to is the really overriding need for particularly rehabilitation in TBI, but I think also TBI generally is to find better ways of differentiating this wide assortment of patients that we have with brain injury.

We saw some very encouraging things today I think. The presentation this morning was great. The fMRI approaches that we heard this afternoon I think are also very encouraging in this regard, but what we really have to do is find a way to start to move beyond categorizing brain injury as minimal, mild, and severe. We need to start getting to the specific injuries that people have and figuring out how to target the therapies to those injuries.

I also wanted to emphasize something else that I heard this morning that we need better models. We do need better models across the board. We need models of all kinds. We need models from the molecular to anatomical to functional and so forth, but what we need along with that and maybe more than that is the linkage from those models to the clinical data that we see, so that we can use those models to make some of the predictions and to identify some of the therapeutic interventions that might actually work.

The last comment I wanted to make -- and this I was sort of reminded of in the conversation with Dr. Dean at the break -- that it is not unusual at this kind of a meeting that when we get around to the point of talking about rehabilitation, the room starts to empty out.

At this point, I presume I am preaching to the choir. I gave her a hard time when she was leaving for exactly that reason. She assured me she had an important meeting that she had to get to, and I am sure that is true.

But what it reminds me of is one of the things that I learned at NIDRR in managing these programs on brain and spinal cord injury, that what we really have to keep in mind, especially these kinds of injuries, is the need for an integrated, comprehensive, continuum of care for individuals from the point of the injury through the emergency room, through the operating room, through acute rehab, and on into long-term rehab, and that is important I think for us to keep in mind not only from the standpoint of care, but also in

looking at the research that we do and how it fits into that continuum and how we can try to make sure that people moving through that continuum progressively over time are going to have a greater preservation and restoration of function.

[Applause.]

DR. CURLEY: Thank you.

Next, I would like to invite Colonel Mary Lopez, Chief, Army Occupational Therapy, Assistant Professor at the Center for Ergonomics and Human Performance at Uniformed Services University of Health Sciences.

Good afternoon.

COL LOPEZ: Good afternoon. Thank you very much.

I think he is right that the room does tend to empty out when you start talking about rehab. Fortunately, that is my bread and butter. I am the occupational therapy consultant for the Army, and that has been an incredible learning experience because we not only are responsible for managing the occupational therapists in terms of assignments, but also in terms of clinical care, standardizing care, ensuring that we are providing the appropriate care, and also establishing policy.

My goal has been to establish as much as possible, evidence-based care, but also to move the research, which we have seen today, forward and applying it to the clinical care. I think there are incredible opportunities for us to drive change, from my position drive care to clinical care.

We all know that traditionally, it takes about 25 year, plus or minus, to get a research evidence-based finding down into clinical care, and my goal, again, has been to shorten that time and push it out as fast as possible to the field.

Right now, we are dealing with quite significant challenges with traumatic brain injury. From a policy perspective, I like to frame things in a certain structure, and so let's analyze what is going on in terms of traumatic brain injury.

The structure I use is PEETSG, and everybody has little acronyms. PEETSG stands for political, ecologic, economic, technologic, sociologic, and geographic, and all of those things are affecting us in terms of policy.

Politically, of course, mild TBI is a significant political issue, and a lot of newspapers these days -- forgive me, but a lot of newspapers these days are actually driving clinical care. That is why you need to forgive me because it is true. It is quite challenging when we are constantly responding to those kind of inquiries.

It is not always the most logical thing to do. It is not always in the patient's best interest, and it is not always in the population's best interest, but politically, it is a very charged, hotly charged issue.

Economically, we are facing a significant problem in our country when the economics of the care for these soldiers that are coming back with mild TBI really starts hitting everyone's pocketbooks. We talk about some additional monies coming into our health care system, and that is important, but I think that that is just the tip of the ice berg in terms of what these conditions will cost society in the long run, in terms of lost wages, in terms of broken families, in terms of just workers who have been affected.

As a side note, I would like to point out also that our entire health care system in the Department of Defense is built on not spending money. I mean, how many times have we heard do more with less, and our whole culture is built around do more with less.

We have incredible folks who provide care under challenging situations because, again, we are doing more with less. So we have a system that has checkpoints in

place with the resource managers and the civilian personnel and the logistics folks, multiple checkpoints to prevent us from spending money, and all of a sudden, Congress has given us $600 million. So you have taken an organization that is traditionally starved, and you have force-fed $600 million into it, and the challenge in actually executing these funds and distributing them and obligating them are quite difficult because, again, our whole system is built up around don't spend money.

The human ecology is something very important to pay attention to because we don't know what the long-term effects of repeated mild traumatic brain injury are on our population.

I can tell you that I have gone down to the medical facilities at multiple bases, and the commanders of these facilities are telling me, "We are very concerned about these soldiers who are coming back." It is not uncommon to have 15, 20, 30, 100 blasts, and they say, "Our soldiers are different. Their wives tell us they are different. Their sergeants tell us they are different. We have more Article 15s," which is another human tragedy. They can't find their way out of the lunch room. They can't remember how to get down to Hollywood Video. We know our soldiers are impaired. We have got a problem, and at one base, they will say, "I have got hundreds and hundreds of soldiers like this," and that is just one base, and then we have got the Fort Drums and Campbells and Hoods and Bliss and everything else. The potential magnitude of what we are facing is significant.

So, again, human ecology in terms of these repeated blasts and these exposures have the potential for being quite significant.

Technologically, we are facing an incredible boom in technology and scientific knowledge about the nature of the brain and rehabilitation and recovery, and so technologically, it is our responsibility to make sure that we drive that out into policy as quickly as possible to, again, prevent as much of that human ecology disaster as possible.

Now, sociologically, this is a very interesting time because, if you go back through history in terms of historic conflicts, World War II we had a different population coming in with different expectations. We had people who had come out of the depression. They were happy to get a job, and you had an entire society that was focused on supporting the soldiers and supporting the war, and everybody shared pain.

My parents will tell me that they didn't have footballs because everybody was conserving rubber at that time, but everybody had a shared pain.

Vietnam happened, and war became very unpopular, and there was a very unpopular draft. So society had a different perspective of the war.

Now we have a volunteer Army. Some people will say because we have a volunteer Army, we have soldiers who are coming in who are theoretically less resilient than other populations. It may or may not be true, but we have definitely different social expectations of the health care system and what is being provided to our soldiers for care.

Again, it is another policy challenge because we are responding to these external influences. I think you know where I am going with this, society's expectations.

I go to the airports, and people will come up. They will shake my hand, in my uniform. They will shake my hand and say, "Thank you very much for serving our country," and they feel good that they thanked me, but there is no shared pain. In general, this is a fairly anonymous war.

Our communities have not felt the impact of these soldiers coming back. However, sociologically, when these soldiers start leaving the WTUs, the war transition units, and they start entering the communities, the communities are not going to understand

the behaviors. The communities are not going to understand why there is more traffic violations or why there is anger or why these soldiers can't handle the stresses of a normal job. We have a potential risk of homelessness, and as I said, broken marriages and everything else.

How do we from a policy perspective, from a system perspective, how do we educate these communities to understand what is going on with this population that is reentering? Again, most of them will reenter.

Geographically, it is another challenge, and again, it goes back to policy, geographically how are we going to get our arms around this because we not only have active components, but we have Reserve and National Guard. Reserve and National Guard folks come out of deployment, and they are only on the ground for a week or less, and then they go back to their communities. Unless we catch them at that week and identify them as soldiers needing care, they have lost an opportunity, a window of opportunity for benefits.

Even if they are identified, they go back into their communities, and now we have a dramatically, geographically dispersed population that needs care. The communities aren't educated on how to provide this kind of medical care that they need. They are not educated on rehabilitation, and all of a sudden, they have this soldier that is dropped into the middle of their community who needs a different kind of care, so how do we push that kind of care into the communities.

Now, in the past, Vietnam, for example, they had installations that were dedicated to rehabilitation, like at Valley Forge, and all of the soldiers with amputations or something else went there. They had an entire culture, a milieu. All of it was focused on rehabilitation, and they had a pretty good result -- pretty good. I mean, we can all argue how the Vietnam War folks came out, but it was pretty good.

Now we have 35 War Transition Units spread across the country. However, we also have families involved. These aren't single soldiers anymore. They have families and parents and people who are going to be coming in and caring for them. How do we establish the standard of care across 35 WTUs? How do we establish a care that is consistent with the care they are going to provide in the VA, and how do we communicate that to the communities, so that they, again, meet that continuum of care?

So my purpose today in just talking about policy is really to outline the challenges that we have with policy and just talk about mild TBI because I think this is something that is going to define how health care is provided, delivered perhaps over the next 15, 20 years because of these unique challenges that we are facing right now.

I think I am up, my 5 minutes, haven't I?

All right. I suppose at the end, we will have questions?

DR. CURLEY: Yes.

COL LOPEZ: Okay. Well, thank you very much for your time.

[Applause.]

Conclusions

DR. CURLEY: Thank you. I want to thank Colonel Lopez.

Actually, the last panelist, it says Joe Pancrazio. That was a typo. He had been committed to another meeting at the time he was invited to do this, and so that should be me. I had already made some comments.

I think Colonel Lopez put things very eloquently policy-wise, and I think for those of you who have been able to stay for the entirety of the meeting, you have heard something of great value as far as that goes.

The issue that concerns me is one that I was just talking to Dr. Thakor about, and that is the chicken and the egg issue. Everybody wants to know, well, did the patient have the behavior first or did they have the injury first, and do we have ten randomized placebo-controlled trials before we allow someone to use such and such therapy, even though we all know from the very get-go that X therapy is beneficial.

It just makes me chew my nails off sometimes in frustration because we are in situations right now where we see therapies. We see systems, the type of systems that Dr. Rosen is working on, for example, that might be very useful for rehabilitation of people with brain injuries, as well as amputations, and we can use these systems and get benefit from them and worry about going back and parsing out this cellular neurophysiology of why they work later.

So policy-wise, I guess that is my main point, even though I have a background from both the clinical and the science side. You might then think that I would want to have everything experimentally proven. I have seen too many examples of tools and methods in the past two years especially that can be of significant use to people now but aren't being used because they haven't met this new demand we have for, quote, "evidence-based medicine."

I think evidence-based medicine is important, but I think you can do a prospective study to show benefit without necessarily having to explain the precise neurobiology behind why a particular therapy works.

So I guess that is the end of my rant. I would like to thank you all for attending today, and I would like to invite the panelists back up. We will take any questions. Paul, you are invited up as well, and we will take any questions that you all might have before we wrap up.

Does anyone have any questions at this point?

ATTENDEE: I have a comment, not a question. I don't know if it has been addressed [inaudible].

DR. CURLEY: I think that is helpful. One of the neat things about work in TATRC is all the cross-over we have. We have a research area that deals with biosensors, and just to be able to see if that might be leveraged to look at something like the monitoring for bladder infection.

ATTENDEE: I think it also echoes the importance of bringing clinicians together with scientists and how challenge that is, though.

We will even see it at Walter Reed. We will bring in top speakers in their fields, cutting-edge engineering or tissue engineering, electrical engineering, and trying to get the clinicians to attend just to stimulate their thought process or interaction with the scientists is difficult in today's environment when everybody is so busy with health care, whether civilian or military. So I think that is a challenge that we all face.

But you are exactly right. More scientist interface with actual providers, I think it makes a big difference, but that means going out to PT meetings, OT meetings, nursing meetings. It is a challenge when we are all busy.

ATTENDEE: [Inaudible.]

ATTENDEE: Both. I have the honor of [inaudible] fortunate perhaps, depending on how you want to frame it, [inaudible]. I was talking about this is a system that is built on starvation, and the roadblocks that I have run into are incredible, but [inaudible] gotten every BCT that we could, and we have [inaudible] policies are being generated from health affairs to do that [inaudible] baseline testing.

The follow-on, of course, is how are we going to manage it for the post-injury [inaudible] problems with [inaudible] are the biggest challenges. Providers want to do this, but just being [inaudible] providers at the right time and the right place is a challenge.

Post-deployment testing. I really would like to invite opinions on this. Post-deployment testing still is an unknown. There is a lot of debate, if we should do 100 percent post-deployment testing or not, and clinicians are kind of going around in a circle, and some of it is from the chicken and the egg that Ken had talked about earlier.

My opinion, what I saw when we did post-deployment testing in Germany, is that it has a definite value. Neurocognitive testing identifies people who need a second look, and it gives you that objective measure that can serve as a baseline.

Some people are seeing it as DNA-type testing that might be used down the road, but [inaudible].

The rehab will follow. We have worked on clinical management guidelines. We have a special postdoc team that just produced a rehabilitation guideline for OT and PT. I don't get the feeling that it has got as much of the science in there as possible, and that is why we really need [inaudible] talking about in those guidelines, but [inaudible] that will reinforce the post-deployment testing [inaudible]. A lot of them are just going back to the evidence-based, show me the multi-centered studies, you know, and make everything comfortable, so I know I am on solid ground before I take that step, and I think we are just going to have to take the steps.

DR. CURLEY: Dr. Thakor?

DR. THAKOR: [Inaudible.]

DR. MYKLEBUST: So you do really want me to talk about IDEs and 510(k)'s? I'm kidding. I'm kidding.

ATTENDEE: [Inaudible.]

DR. MYKLEBUST: I think that the design of -- there's a couple of aspects that I think are important here. One, the design of clinical trials I think is an ongoing, evolving area that we really need to look at in the context of some of these therapeutic devices and products and applications that we are looking at.

I think there is a growing realization that the sort of standard RCT kind of thing is not always the way that these things have to be done.

The other thing, I think for a lot of the things that we are talking about, even though we look at the numbers for head injury and we come up with numbers pretty quickly in the millions, we are often dealing with things that are applicable to smaller populations, and it is important to keep in mind the humanitarian device exemption approach that the FDA has.

ATTENDEE: Just the revolutionary prosthetics program, we are waiting for a couple arms to put them on patients. There's some pretty well-validated hand function tools that you can do that are functionally based. You can do pre and post fitting and get some pretty powerful data.

Now, is that going to change the industry, and is that going to change third-party payment? Well, if you can get a couple of them on the Today Show or ABC, NBC, on mainstream TV showing a revolutionary improvement in function, then everybody would be -- there would be so much pressure on insurance companies to cover things like that. That is kind of I think where we're headed, but you got to show a big difference, and I think that is the challenge to all of us. So people go about that cautiously because you don't want to over-promise and under-deliver.

But it is exciting stuff, and we are looking forward to it. That is easier than deep brain stimulation. That is easier than some of the more invasive techniques. So I don't see that being that difficult.

DR. CURLEY: I think one of the challenges from the perspective of the upper extremity is that there aren't a lot of metrics as far as assessing function, especially now that you are talking about 21-degree-of-freedom arms. I think that is posing a challenge, too.

One of the groups that I am working with out to Cleveland, it is working with basically a functional electrical stimulation-based system or controlling a commercial myoelectric arm. They went through a number of different assessment tools, and first, there were probably only about six or seven tools that they could find, and out of those, there were two that applied with any kind of validity to the arm itself.

So you are in somewhat novel territory simply because the upper extremity above-elbow amputation is so relatively rare. Some of us have wondered if because of that rare nature outside of the military situation that it might not end up really an orphan situation while the military is having to just buy these one at a time versus there ever being a market. I have a hard time seeing a prosthetics company picking something like that up, no matter how much good it might do, simply because of the cost of having to tool up to build those versus the number of them that you sell in a year. In that case, it comes down to sheer business. [Inaudible] look beyond that trying to look at restoring function and quality of life, which I don't necessarily feel you can put a price on.

ATTENDEE: [Inaudible.]

ATTENDEE: I wanted to second the point about the focus on the individual, but I also wanted to thank Colonel Lopez for reminding us of one of the fundamental parts of rehabilitation I think which is that a lot of times, it ends up that we can't fix the individual, and then we need to fix the environment. That is whether it is curb cuts or captioned televisions. It is also the social environment in our institutions. I think that is a really important point.

DR. CURLEY: Thank you.

Well, I think with the weather turning sour, that is about it. I want to thank everybody again for coming today. Once again, I would like to thank AIMBE for having us and thank my speakers and my panelists. Thank you, Warren.

Do you have any comments, Warren?

DR. GRUNDFEST: Just a few brief closing remarks because it is late, and people want to get going. I want to thank everybody who came. I think this is an excellent example of bringing clinicians, engineers, and scientists together. It is what I hope to do more with AIMBE and TATRC. I will be contacting people in the future to see if we can put together a follow-on meeting.

With that, thank you very much for attending.

[Applause.]

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Appendix C
AIMBE Press Release

Bioengineering on Front Lines In Assessing, Treating War-Related Brain Trauma

Special Panels at the Annual Event Examine Challenges, Opportunities

The medical challenges presented by modern warfare struck home at AIMBE'S Annual Event in Washington, DC, during February – and were answered with views of the promise medical and biological engineering hold for addressing the war's physical impact on soldiers.

During *AIMBE-Military Collaboration: Bioengineering Challenges of Brain Trauma*, a day-long seminar at the National Academy of Sciences in which a team of military and civilian experts, including several AIMBE Fellows, looked at important new technologies addressing what has been called the "signature wound" of the war on terrorism.

The session was the brainchild of AIMBE Fellow Warren Grundfest, M.D., F.A.C.S., a professor at the University of California, Los Angeles. He wanted to provide a forum for AIMBE members and other leaders in the field of medical and biological engineering to discuss this important topic and identify the most important areas for future work. Grundfest spearheaded AIMBE's co-sponsorship of the event with the U.S. Army Medical Research and Materiel Command's Telemedicine and Advanced Technology Research Center (TATRC).

TATRC's Chief Scientist, Kenneth C. Curley, M.D, was Grundfest's partner in planning the event and assembling its panel of more than 20 distinguished speakers. TATRC is responsible for a broad array of advanced and developing technologies to meet military medicine requirements.

In Afghanistan and Iraq, body armor saves many soldiers from fatal injuries they might have suffered in earlier conflicts, but the head remains vulnerable. Aside from ongoing work to improve protective equipment, military healthcare providers face a two-fold challenge – identifying and assessing the extent of brain trauma from attacks on the battlefield, then treating the injury effectively once a soldier reaches a hospital.

Army COL Geoffrey Ling, M.D., Ph.D., noted that traumatic brain injury (TBI) "has always been there" – historically accounting for 15-20 percent of battle-related casualties. In the past, Ling said, it was often assumed that a soldier would die from a severe head injury, but new technologies and procedures allow military doctors to focus on brain trauma treatments and save many of their patients.

"Mild TBI" – often resulting from a blast shockwave, with no visible head injury – also is a concern, according to Ling, who is Program Manager in the Defense Sciences Office of the Defense Advanced Research Projects Agency. "We don't know what that number is," he

said, but estimated that 25-40 percent of soldiers in Iraq and Afghanistan may have suffered a closed head injury.

Navy Commander Jack Tsao, M.D., D.Phil., Associate Professor of Neurology at the Uniformed Services University of the Health Sciences, noted that one of the greatest head injury threats in the current war comes from improvised explosive devices (IEDs), the "roadside bombs" often cited in news accounts. He cited statistics from Walter Reed Army Medical Center showing that, as of summer 2007, 30 percent of patients requiring medical evacuation for battle-related injuries from the war zone to Walter Reed had TBI.

Tsao noted that, while penetrating head injuries are typically identified and cared for immediately, "non-penetrating, or closed, TBI' (where there is no piercing of the skull) may be missed when more visible injuries to other body parts require immediate attention.

Touching on another theme, Tsao noted that, "There is an overlap between PTSD (post-traumatic stress syndrome) symptoms and mild traumatic brain injury symptoms." During the program, several other speakers also touched on the on-going discussion of how best to identify that line so that patients can receive appropriate treatment.

Much of the discussion was devoted to the appropriateness – and portability – of various imaging technologies in assessing the different types of brain injuries suffered by soldiers.

Ling noted that field-capable diagnostics are needed to help assess the true extent of injuries and manage prompt treatment in the field. "You can't wait for a radiologist," he said. "You need simple, deployable diagnostics devices at the point of care."

Tsao pointed out that imaging at major field hospitals in the war zone is limited to X-Ray and CT scanning, and examined efforts to improve TBI detection through use of portable CT, MRI, TCD, NIRS, or other methods.

Mark S. Cohen, Ph.D., of the University of California, Los Angeles, discussed the development of a new approach to magnetic resonance imaging (MRI) that will greatly reduce the size, weight, cost and complexity, improving access both in combat support and in health management of injured soldiers, many of who require followup imaging.

Rather than detect the magnetic resonance signals by electromagnet induction, the device Cohen described uses Superconducting Quantum Interference Detectors (SQUIDs) as pickups. These allow the MRI unit to operate effectively at very low magnetic field strengths. MRI is particularly important in the followup of concussive incidents that may lead to TBI.

Cohen said MRI is generally acknowledged to be both more sensitive and more specific in assessing such injuries, but that practical problems such as cost, scheduling and transport limit its use. He believes that the Ultra Low Field MRI will mitigate these problems.

Alisa D. Gean, M.D., Professor of Radiology, Neurology and Neurological Surgery at the University of California, San Francisco, and Chief of Neuroradiology at San Francisco General Hospital, stressed the importance of portable imaging equipment in reducing the

stress patients endure in being moved from their beds to a separate room with fixed imaging devices.

She also said CT equipment is superior to MRI technology in assessing many of the war's most prevalent injuries – particularly when a patient has been peppered with shrapnel from an IED.

Gean said mobile equipment is easy to operate, can be run from a conventional 120-volt wall outlet or even a battery, is compact and does not require shielding of the room, performs axial and coronal images quickly, and can provide CTA and 3D images.

Several speakers said they support proposals to collect MRIs of the brains of all soldiers when they enter the military, to serve as benchmarks against scans taken later when brain trauma is thought to have been suffered on the battlefield.

Curley praised the session as "an opportunity for national leaders in the fields of neurotrauma diagnostics and therapeutics to meet, exchange ideas and obtain feedback from their biomedical engineering colleagues."

"Development of medical technologies is increasingly multidisciplinary," Curley noted. "The AIMBE session resulted in valuable feedback from experts across many disciplines regarding what technologies are most promising and how they might best be further developed."

Appendix D
Program Document

AIMBE-Military Collaboration:

Bioengineering Challenges of Brain Trauma

Wednesday, February 20, 2008

National Academy of Sciences Lecture Room

Hosted by

American Institute for Medical and Biological Engineering

and

US Army Medical Research and Materiel Command
Telemedicine and Advanced Technology Research Center

Agenda

National Academy of Science
Lecture Room
21st and C Streets, NW

Wednesday, February 20, 2008
8:00 a.m. to 4 p.m.

8:00 a.m.	*Introduction and Welcome* **Warren Grundfest, M.D., F.A.C.S.,** Meeting Co-Chair Professor, University of California, Los Angeles
	Kenneth C. Curley, M.D., Meeting Co-Chair Chief Scientist, US Army Medical Research and Materiel Command Telemedicine and Advanced Technology Research Center
	Geoffrey Ling, M.D., Ph.D., Meeting Co-Chair Program Manager, Defense Advanced Projects Agency
8:30 a.m.	*Imaging: The Current State of Technology and Challenges* **Jack Tsao, M.D., Ph.D.,** Session Chair Principle Investigator Uniformed Services University of the Health Sciences
8:45 a.m.	*Diffusion Tensor Imaging in Traumatic Brain Injury* **Marilyn F. Kraus, Ph.D.,** Associate Professor of Psychiatry and Neurology, University of Illinois at Chicago
9:00 a.m.	*The Use of Portable Field SQUID Devices* **Mark S. Cohen, Ph.D**., Professor in Residence University of California, Los Angeles, School of Medicine
9:15 a.m.	*CT and its Role in Portable Field MRI* **Alisa D. Gean, M.D.,** Professor of Radiology, Neurology and Neurological Surgery, University of California, San Francisco; Chief of Neuroradiology, San Francisco General Hospital
9:30 a.m.	*Study of Cerebral Functioning with Near Infrared* **Andreas H. Hielscher, Ph.D.,** Associate Professor of Biomedical Engineering, Columbia University
9: 45 a.m.	*Panel Discussion: Policy Implications* **Seong K. Mun, Ph.D.,** Director and Professor of Radiology Director of the Imaging Science and Information System (ISIS) Research Center Georgetown University Medical Center **Ron Kikinis, M.D.,** Director of the Surgical Planning Laboratory, Professor of Radiology, Harvard Medical School **Larry Clarke, Ph.D.,** Cancer Imaging Program, National Cancer Institute
10:30 a.m.	Break
10:45 a.m.	*Monitoring: The Current State of Technology and Challenges*

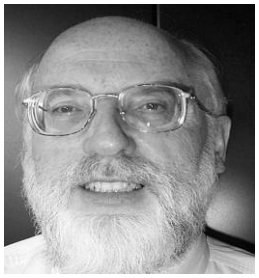
	Colonel Geoffrey Ling, M.D., Ph.D., Session Chair, Program Manager, Defense Advanced Projects Agency
11:00 a.m.	*Challenges and New Devices for Noninvasive ICP Monitoring* **R. Daniel Ferguson**, Principle Research Scientist, Physical Sciences, Inc.
11:15 a.m.	*Use of Biomarkers to Assess Cerebral Status* **David Hovda, Ph.D.,** Professor of Surgery, University of California, Los Angeles
11:30 a.m.	*Real Time (Acoustic) Monitoring of the Brain* **Richard Dutton, M.D., MBA,** Associate Professor of Anesthesiology University of Maryland Medical System
12:00 a.m.	Lunch
1:00 p.m.	*Panel Discussion: Policy Implications* **Ronald Hayes, Ph.D.,** Chief Clinical Programs Officer, Founder, Banyan Biomarkers **David Moore, M.D., Ph.D.,** Director of Research Defense and Veterans Injury, Walter Reed Army Medical Center **Pierre Mourad, Ph.D.,** Adjunct Professor University of Washington
1:30 p.m.	Break
1: 45 p.m.	*Rehabilitation Therapeutics: The Current State of Technology and Challenges* **Lieutenant Colonel Paul F. Pasquina, M.D.,** Session Chair, Chairman, Physical Medicine & Rehabilitation, Walter Reed Army Medical Center
2:00 p.m.	*The Development of Neuroprosthetics in Rehabilitation* **Nitish Thakor, Ph.D.,** Professor of Biomedical Engineering, Johns Hopkins University
2:15 p.m.	*Tissue Engineering and Regenerative Medicine CNS as an approach to Rehabilitation* **Smita Savant-Bhonsale, Ph.D.,** Vice President and General Manager, Theradigm, Inc.
2:30 p.m.	*Use of Robotics for Physical Rehabilitation* **Jacob Rosen, Ph.D.,** Research Associate Professor, University of Washington
2:45 p.m.	*Use of fMRI to Assess Brain Function during Rehabilitation* **Scott Frey, Ph.D.,** Director of the Lewis Center for Neuroimaging University of Oregon
3:00 p.m.	*Panel Discussion: Policy Implications* **Colonel Mary Lopez**, Chief, Army Occupational Therapy, Assistant Professor, Center for Ergonomics and Human Performance at Uniformed Services **Joel Myklebust, Ph.D,** Director, Division of Physics, Food and Drug Administration **Joseph Pancrazio, Ph.D.,** Program Director , Extramural Research Program, NIH National Institute of Neurological Disorders and Stroke

3:30 p.m. *Conclusion*
Kenneth C. Curley, M.D., Meeting Co-Chair
Chief Scientist, US Army Medical Research and Materiel Command
Telemedicine and Advanced Technology Research Center

Warren Grundfest, M.D., F.A.C.S., Meeting Co-Chair
Professor, University of California, Los Angeles

Geoffrey Ling, M.D., Ph.D., Meeting Co-Chair
Program Manager, Defense Advanced Projects Agency

Speaker Biographies



Laurence Clarke, Ph.D.

Dr. Clarke as of January 1999 is the Branch Chief for Imaging Technology Development for the Biomedical Imaging Program (BIP), Division of Cancer Treatment and Diagnosis, NCI, NIH. In this capacity he is responsible for development of initiatives for supporting new and emerging imaging technology, involving both academia and industry, as applied to cancer. His responsibilities also include the development of initiatives that support research resources for assessing new imaging methods including the development of international resources for evaluation of image processing algorithms. Dr. Clarke has a detail assignment at NIBIB since 2005 and a Visiting Scientists Position at NIST as of Aug 2006 and is being tasked to develop standards for biomedical imaging for therapy response from a hardware and software perspective.

Before joining NCI, Dr Clarke was a Professor of Radiology and Adjunct Professor Physics and Computer Science at the University of South Florida (USF), and Program Leader for Digital Medical Imaging Program at the H. Lee Moffitt Cancer and Research Center at USF. He has previously worked at other cancers centers at the University of Miami and the Memorial Sloan Kettering Cancer Center NYC. Dr. Clarke has been active over the last 30 years in the area of image processing for early cancer detection, cancer diagnosis and treatment response for a range of imaging modalities. He is a Fellow of the ISMRM (1994) and AAPM (1990). He graduated with a Ph.D. in medical physics at the National University of Ireland (1978) and an MS degree in Pure and Applied Physics from Queens University of Belfast, Ireland (1968).

Mark S. Cohen, Ph.D.

Mark S. Cohen is a Professor in the departments of Psychiatry, Neurology, Radiology, Biomedical Physics and Psychology at UCLA. His work, broadly, is on the development of imaging technologies, principally MRI, targeted towards identified problems in neuroscience and clinical medicine. He was among the earliest proponents and developers of echo planar imaging, functional MRI (fMRI) and multimodality acquisition combining imaging and electrophysiological data. Mark was the Director of Education for the Society of Magnetic Resonance Imaging and directs a training program in neuroimaging at UCLA. His current interests include multidimensional data analysis, ultra-low field imaging and real-time MRI.

Colonel Kenneth Curley, M.D.

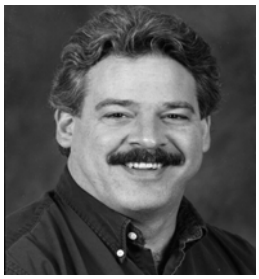
Kenneth C. Curley, M.D. received his Bachelor of Science in Biology (Molecular Biology/Pre-Med) Cum Laud from John Carroll University, Cleveland, Ohio. He was concurrently commissioned Second Lieutenant, USA, after a four-year ROTC scholarship. He received his M.D. from Uniformed Services University of the Health Sciences (USUHS), Bethesda, MD in 1993.

Dr. Curley's post-graduate training began in 1993 as a surgical intern at Walter Reed Army Medical Center. He then completed a Pediatric internship in 1994 as part of the Academic Adult and Child Neurology residency pathway at WRAMC with a two-year assignment as a Medical Research Fellow and Principal Investigator, Dept. of Neuropharmacology and Molecular Neurobiology, Walter Reed Army Institute of Research. In 1997 he returned to WRAMC for the clinical neurology portion of his training. During this period, Dr. Curley sustained a spinal cord compression injury. While he underwent treatment, he served as a medical informaticist, clinical research associate, and continuing medical education coordinator for the Departments of Neurosurgery at National Naval Medical Center and WRAMC. He received command appointments to medical information technology and quality assurance committees at NNMC and DoD. He assisted in the development of the DoD's first image-based diagnostics and computer-assisted surgical planning lab at NNMC. He developed knowledge, skills and experience in image-guided surgery technologies, advanced medical imaging processes including 3-D volumetric imaging, image fusion, and virtual endoscopy. Dr. Curley then served as a research associate and resident in the Department of Radiology, WRAMC. He reported to TATRC in November, 2000 as a Clinical Consultant and Technology Analyst for biomedical engineering aspects of imaging, surgery, and medical modeling and simulation. He also serves as a subject matter expert in tissue engineering, and neuroprostheses. He was medically retired from the Army in October 2002 and returned to TATRC in May 2003 as an IPA with the Henry M. Jackson Foundation for the Advancement of Military Medicine, and was appointed Chief Scientist in April, 2004. In 2006 he developed and became manager of the Neuroscience research portfolio. Dr. Curley serves on numerous intergovernmental research and development working groups including modeling and simulation, image guided therapies, tissue engineering and neuroprosthetics. Dr. Curley is Assistant Professor of Military and Emergency Medicine, Surgery and Biomedical Informatics, and serves as Special Assistant to the Director, Center for Disaster and Humanitarian Assistance Medicine at USUHS.

Richard Dutton, M.D., MBA

Richard P. Dutton, M.D., MBA is an Associate Professor in the Department of Anesthesiology at the University of Maryland (UMD), School of Medicine. He is the Director of Trauma Anesthesiology at R. Adams Cowley Shock Trauma Center at UMD.

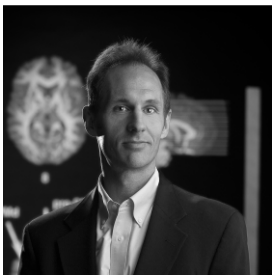
Dr. Dutton received his medical degree from the School of Medicine at Tufts University. He completed his residency at Massachusetts General Hospital. He is currently the Editor-in-Chief of the ASA's Self-Education and Evaluation program. His numerous scholarly publications span the range of trauma anesthesiology and reflect his interests in resuscitation from hemorrhagic shock, management of traumatic brain injury, and hospital trauma care systems.



R. Daniel Ferguson

Dan Ferguson received his B.S. and M.S. degrees in Physics from the University of Akron in 1979/81. Mr. Ferguson continued graduate work at Cornell University developing optical diagnostic devices and received an M.S. in Physics in 1985. He joined Physical Science Inc (PSI) in 1987 (and has just celebrated his 20th anniversary there) where he has continued to invent, develop, and apply unique optical instrumentation and novel biomedical sensors in many interdisciplinary research programs. Over the

years, Mr. Ferguson's diverse research interests have led to improved understanding of polymer physics with magnetic resonance techniques, turbulent vorticity fields in fluids, acoustic propagation in complex materials, and laser/material interactions. Mr. Ferguson's main R&D activities are currently in biomedical optics diagnostic system, including advanced eye tracking for scanning laser ophthalmoscopy (TSLO) and for Optical Coherence Tomography (TOCT), a compact, hand-held line scanning laser ophthalmoscope (LSLO), hybrid field-portable LSLO/OCT instruments, Adaptive Optics (AO) imagers, and research exploring the properties and diagnostic applications of ocular hemodynamics. Some of Mr. Ferguson's inventions have been licensed to a major ophthalmic instrument manufacturer and are now used routinely in the clinic.



Scott H. Frey, Ph.D.

Scott received a Masters degree from Harvard in 1987 in Human Development and a Ph.D. from Cornell in Experimental Psychology in 1993. His current work explores the neural bases of perception and action in humans, with particular attention to complex manual skills such as prehension, tool use and gesture. A major focus of this work is to advance our understanding of how brain organization is affected by upper limb paralysis or amputation as well as the role that cognitive training and/or use of prostheses might play in functional reorganization. His approach is to seek convergent evidence through psychophysical, functional (fMRI) and structural MRI, and MRI-guided transcranial magnetic stimulation (TMS) studies of healthy and patient populations.

Alisa Gean, M.D.

Alisa D. Gean, M.D. is a Professor of Radiology, Neurology, and Neurosurgery at the University of California, San Francisco. She currently serves as the Chief of Neuroradiology at San Francisco General Hospital.

Dr. Gean obtained both her BS and MD degrees at Stanford University. She then completed an Internal Medicine Internship at San Francisco Children's hospital, followed by a Residency in Diagnostic Radiology at Massachusetts General Hospital and Harvard Medical School, and a two-year Fellowship in Neuroradiology at the Massachusetts General Hospital and Harvard Medical School.

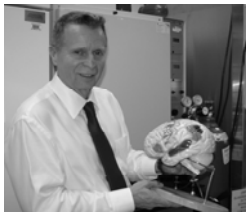
She joined the faculty at UCSF in 1989 as the Chief of Neuroradiology at San Francisco General Hospital. She is a senior member of the American Society of Neuroradiology and obtained her CAQ in 1996. Dr. Gean is also an examiner for the American Board of Radiology. Dr. Gean's editorial activities include JAMA, American Journal of Neuroradiology, Radiology, Journal of Trauma, Annals of Neurology, Journal of Neuro-AIDS, and the Journal of Computed Assisted Tomography.

Dr. Gean's primary professional interests include central nervous system trauma, stroke, and HIV disease. She lectures nationally and internationally on the topic of traumatic brain injury, and is a founding member of the Brain and Spine Injury Center ("BASIC") at UCSF. Dr. Gean has written extensively on the topic of TBI, and is the sole author of the internationally recognized textbook, "Imaging of Head Trauma". She currently serves on NIH and CDC committees to evaluate the imaging approach to TBI.

Warren Grundfest, M.D., F.A.C.S

Warren Grundfest is a professor at UCLA in the Department of Bioengineering. Excimer Lasers for Medical Applications. The laser research

lab has pioneered the development of pulse ultra-violet of excimer lasers for biomedical applications. We continue to investigate cardiovascular, ophthalmologic, orthopaedic and neurosurgical application of this technology. Biologic spectroscopy, the use of spectral data to identify and classify tissue is another major focus of our research. We employ multiple techniques including time resolved spectroscopy, hyperspectro-imaging, photo bleaching and laser attenuation spectroscopy for the study of biologic systems. Clinically, we are actively involved in the development of minimally invasive imaging and surgical tools.



Ronald L. Hayes, Ph.D.

Dr. Ronald L. Hayes received a Ph.D. in Physiological Psychology from Virginia Commonwealth University in 1975. He also served as a fighter pilot in the Virginia Air National Guard. In October, 2007, he resigned from the University of Florida and began working full time in the company he founded, Banyan Biomarkers, Inc. He has established the Center of Innovative Research which focuses on laboratory studies of basic mechanisms of traumatic brain injury and development of novel therapies to treat deficits following brain injury including disturbances in memory and attention. Dr. Hayes has published more than 210 peer reviewed papers and 45 book chapters. He has been continuously funded by the NIH for almost 20 years and is currently funded by both the NIH and the Department of Defense.

Andreas H. Hielscher, Ph.D.

Andreas H. Hielscher received his Ph.D. degree in Electrical and Computer Engineering from Rice University, Houston, Texas, in 1995. After spending 2 years as Postdoctoral Fellow at the Los Alamos National Laboratory in New Mexico, he joined the faculty at the State University of New York Downstate Medical Center in Brooklyn, New York. In September 2001 he moved to Columbia University in New York City, where he is now the Director of the Biophotonics and Optical Radiology Laboratory. He holds joint appointments as Associate Professor in the Departments of Biomedical Engineering and Radiology.

Dr. Hielscher made pioneering contribution in the field of Biomedical Optics. His work currently focuses on the development of state-of-the-art imaging software and hardware for optical tomography. He applies this emerging technology to imaging of cancer and joint diseases and uses it in support of drug development. He has published over 120 articles in peer-reviewed scientific journals and conference proceedings. Dr. Hielscher's work has been funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Heart, Lung, and Blood Institute (NHLB), the National Institute for Biomedical Imaging and Bioengineering (NIBIB), the National Cancer Institute (NCI), the Whitaker Foundation for Biomedical Engineering, and the New York State Office of Science, Technology and Academic Research.

Dr. Hielscher currently serves as Associate Editor of the IEEE Transactions of Medical Imaging and has reviewed papers for over 30 scientific journals, including the Journal of Biomedical Optics, Optics Letters, IEEE Transactions on Biomedical Engineering, Medical Physics, Physics Review Letters, and Review of Scientific Instrumentation. He has been active in organizing conferences and meetings that promote the field of Biomedical Optics on more than 20 occasions. Among others, he was Chair of the Biomedical Optical Spectroscopy Group at the Optical Society of America (OSA) from October 2001 – 2003, and chaired symposia and sessions on optical imaging at the IEEE –EMBS conferences in 1997, 1998, 1999, and 2005. His is currently a member of the SPIE Medical Imaging Conference Program Committee on "Physiology, Function, and Structure from Medical Images," and the OSA Conference Program Committee for "Advances in Optical Imaging and Photon Migration." In addition he frequently serves on review panels for the National Institutes of Health (NIH)and National Science Foundation (NSF) as well as several international funding agencies, such as the British

Welcome Trust or Dutch Organization for Scientific Research. He is listed in Marquis Who's Who in America since 2005.

David Hovda, Ph.D.

Dr. Hovda is the Director of the UCLA Brain Injury Research Center. He is a former President and current President – Elect of the National Neurotrauma Society and study section committee chair for the National Institute for Neurological Disease and Stroke (NINDS). He is the current chair for the Brain Injury and Neurovascular Pathologies study section for the NINDS and has been elected President of the International Neurotrauma Society (2009-2012). Dr. Hovda has received a number of awards for his research on brain injury and recovery of function, including the 1991 National Head Injury Foundation Award, the Giannini Foundation Award, the Benjamin Franklin Haught Memorial Award and named the Lind Lawrence Eminent Scholar for his work on the topic of Traumatic Brain Injury. In addition Dr. Hovda received the 2006 Women in Neurotrauma award for his teaching and support for women in neuroscience. Dr. Hovda is most well known internationally for his translational work on the pathobiology of traumatic brain injury. He has devoted most of his career to understanding the mechanisms of recovery of function. He currently sits on several editorial boards including the journals **Restorative Neurology and Neuroscience**, **The Journal of Neurotrauma, The Journal of Cerebral Blood Flow and Metabolism** and **Developmental Brain Dysfunction**. He is often invited to lecture at other universities and consults for several different national programs including the Department of Defense, addressing issues related to developing therapeutic treatments for traumatic brain injury.

Dr. Hovda received his doctoral training at the University of New Mexico under the supervision of Dr. Dennis M. Feeney. His 1985 doctoral thesis described how amphetamine administration can restore binocular depth perception after damage to the visual cortex. Dr. Hovda was then recruited by UCLA to conduct work looking at the effect that injury to the brain has on development. This work resulted in several discoveries addressing how the young brain can reorganize itself in order to enhance recovery of function after it has been damaged. In 1989, Dr. Hovda was recruited by the Division of Neurosurgery to direct its scientific efforts to understand the cellular pathophysiology of brain injury. This work resulted in providing the backbone for UCLA being recognized as a "Center of Excellence" by the National Institutes of Health.

Dr. Hovda was born in 1953 in Tomah Wisconsin but spent most of his time in Albuquerque New Mexico. He attended the University of New Mexico during the 1970s playing on the golf team for a short period. Currently he still is an avid player and continues to compete. In 1979 he married Cydney C. Stewart, M.D. who is a cardiologist currently practicing at Woodland Hills Kaiser Hospital in Los Angeles.

Ronald Kikinis, M.D.

Dr. Kikinis is the founding Director of the Surgical Planning Laboratory, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, and a Professor of Radiology at Harvard Medical School. This laboratory was founded in 1990.

Dr. Kikinis is the Principal Investigator of the National Alliance for Medical Image Computing (NA-MIC, a National Center for Biomedical Computing, an effort which is part of the NIH Roadmap Initiative), and of the Neuroimage Analysis Center (NAC a National Resource Center funded by NCRR). He is also the Research Director of the National Center for Image Guided Therapy (NCIGT), which is jointly sponsored by NCRR, NCI, and NIBIB.

During the mid-80's, Dr. Kikinis developed a scientific interest in image processing algorithms and their use for extracting relevant information from medical imaging data. Since then, this topic has matured from a fairly exotic topic to a field of science. This is due to the explosive increase of both the quantity and complexity of imaging data. Dr. Kikinis has led and has participated in research in different areas of science. His activities include technological research (segmentation, registration, visualization, high performance computing), software system development (most recently the 3D Slicer software package), and biomedical research in a variety of biomedical specialties. The majority of his research is interdisciplinary in nature and is conducted by multidisciplinary teams. The results of this research have been reported in a variety of peer-reviewed journal articles. He is the author and co-author of more than 230 peer-reviewed articles.

Before joining Brigham & Women's Hospital in 1988, he trained as a researcher in computer vision at the ETH in Zurich and as a resident in radiology at the University Hospital in Zurich, Switzerland. He received his M.D. degree from the University of Zurich, Switzerland, in 1982.

Marilyn F. Kraus, M.D.

Marilyn F. Kraus, M.D is an Associate Professor of Psychiatry and Neurology at the University of Illinois at Chicago. She completed medical school and residency at Tulane in New Orleans, and completed two fellowships, at Baylor College of Medicine in Houston and at Johns Hopkins in Baltimore. She has worked in the area of traumatic brain injury (TBI), both clinically as well as in research, for over 15 years. She is currently NIH funded to study traumatic brain injury (TBI), and several projects are ongoing. Her research has focused on the neuropathology and neurobehavioral outcomes of TBI using diffusion tensor imaging (DTI), functional MRI and oculomotor studies. Dr. Kraus has had multiple publications in this area, and she lectures frequently. She also currently runs a clinic for the evaluation and treatment of disorders of cognition, mood and behavior due to TBI, with a focus on neuropharmacologic interventions.

Colonel Geoffrey Ling, M.D., Ph.D.

COL Geoffrey Ling, MC, USA is a program manager at the Defense Advanced Projects Agency. At the agency, his focus has been on improving warfighter survival from combat related injury. There his program portfolio included Advanced Prosthesis (neural controlled robotic arm), Preventing Violent Explosion Neurotrauma (elucidating the physical mechanism by which IEDs cause traumatic brain injury and mitigating it), Human Assisted Neural Devices (brain control of assistive devices), Freeze Dried Platelets and others.

COL Ling is the only practicing neuro critical care specialist in the U.S. military. In that capacity, he has been deployed to both Operation Enduring Freedom (Afghanistan) and Operation Iraqi Freedom. In Afghanistan, he served with the 452nd Combat Support Hospital and in Iraq, he served with the 86th Combat Support Hospital, “the Baghdad ER,” and the 10th Combat Support Hospital, where he was “the physician of the month” in November, 2005.

He is also Professor and Vice-Chair of Neurology at the Uniformed Services University of the Health Sciences (USUHS) in Bethesda, Maryland as well as an attending physician at Walter Reed Army Medical Center and Johns Hopkins Hospital.
Dr. Ling earned his undergraduate degree from Washington University, his Ph.D. at Cornell University and his Medical Degree from Georgetown University School of Medicine. Following a medical internship and residency at Walter Reed Army Medical Center, he completed fellowships in

Neuroscience Critical Care at Johns Hopkins University in Baltimore, MD and in Neuropharmacology at Memorial Sloan-Kettering Cancer Center in New York.

Dr. Ling's research interests are mainly focused on brain injury – trauma and stroke. His laboratory at USUHS takes a broad approach to injury. Studies are done developing new diagnostic imaging approaches, novel pharmacologic agents and elucidating mechanisms of brain edema formation. He has authored over 50 journal articles and 35 reviews/book chapters, including Cecil's Textbook of Medicine.

David Moore, M.D., Ph.D.

Dr. Moore is a certified neurologist with extensive expertise in neuro-imaging, fluid dynamics, bio-informatics and mathematical biology. He has previously carried out investigations involving transcranial Doppler (TCD), positron emission tomography (PET), arterial spin tagging (AST), laser Doppler flow studies, magnetic resonance elastography (MRE), peripheral vessel M mode and B mode ultrasound scanning, analysis of neuro-imaging data, gene microarray data and UNIX system administration. Dr Moore trained at Imperial College (London), New York Hospital and the National Institutes of Health (Bethesda, Maryland). He is currently Director of Research, Defense and Veterans Brain Injury, headquartered at Walter Reed Army Medical Center, Washington DC.

Pierre Mourad, Ph.D.

Dr. Mourad holds joint appointments within the Applied Physics Laboratory and the Departments of Neurological Surgery and Pediatric Dentistry (Adjunct) at the University of Washington.

He received a BA in Mathematics from Rutgers University and MSc and Ph.D. degrees in Applied Mathematics from the University of Washington. He has performed and published basic and applied research in oceanography, atmospheric sciences, sonoluminescence, arctic and ocean acoustics, acoustic holography and medical acoustics. Supporting this work have been organizations such as DARPA, NASA, NIH, NSF, ONR as well as from private industry. Medical applications of ultrasound has been his professional emphasis for about the last ten years. In addition to his peer-reviewed publications, he has generated greater than thirty invention disclosures at the University of Washington. He is listed as an inventor on four issued patents and another thirteen patent applications, all having to do with means of diagnosing or treating a variety of diseases and disorders. Much of his research is collaborative in nature, residing as it does at the interface of physics and medicine; some of that research has motivated industrial interactions. For example, his research on novel means of facilitating drug delivery has been incorporated into two recent startup companies in the NorthWest, specifically Inson Medical and PhaseRx. His research on a novel power toothbrush that also uses ultrasound resides in Ultreo Inc, a company he co-founded. Finally, he co-founded Allez PhysiOnix Ltd, based on his research on monitoring intracranial pressure non-invasively, automating ultrasound Doppler systems, and improving physician's ability to localize painful tissues and organs.

Seong K. Mun, Ph.D.

Seong K. Mun, Ph.D., Professor of Radiology and Professor of Immunology, is the Director of the Imaging Science and Information System (ISIS)

Research Center, Georgetown University Medical Center. Established in the 1980s to develop the picture archiving and teleradiology capabilities for the US Army, the ISIS Center has grown to approximately 100 faculty and staff who pursue research and development in imaging, informatics, medical robotics, and global disease surveillance. Dr. Mun's research deals with the role of imaging and information technology in a variety of healthcare settings such as diagnostic imaging, chronic illness management, home monitoring, telemedicine, disease surveillance, surgical instrumentation, and cancer therapy. In March 2007, he is hosting a national conference at Georgetown University to review the new opportunities and challenges of longitudinal electronic health record. As an Associate Vice President at the Georgetown University Medical Center, he is responsible for developing strategic research programs such a gynecological oncology, neurosurgical research and drug development.

Dr. Mun received his doctoral degree in physics for his research in the electronic properties of hemoglobin at the State University of New York, Albany. His postdoctoral fellowships include training in medical physics at the University Of Colorado Medical Center and MRI contrast development research training in Dr. Lauterbur's lab at the SUNY, Stony Brook. In the early 80's, he led the development of one of the first 1.5T high field whole body MRI systems at Columbia University Medical Center in New York City. He is a recent recipient of Thurman Award by the US Army for his research contribution in telemedicine and advanced medical technology. He is a member of AIMBE.

Joel B. Myklebust, Ph.D.

Dr. Joel Myklebust is currently the Director of the Division of Physics in the Office of Science and Engineering Laboratories (OSEL). OSEL is part of the Center for Devices and Radiological Health in the Food and Drug Administration. In this capacity, Dr. Myklebust oversees research on electrophysiology and electrical stimulation, optical therapeutic and diagnostic devices, and the effects of electromagnetic interference on medical devices. Before joining the FDA in 2005, he was at the National Institute on Disability and Rehabilitation Research (NIDRR) with a particular focus on rehabilitation engineering. He was previously on the faculty in Biomedical Engineering at Marquette University and led research laboratories at the Veterans Affairs Medical Center and the Medical College of Wisconsin in Milwaukee, Wisconsin. Dr. Myklebust has a B.S. and M.S. in Electrical Engineering, and a Ph.D. in Biomedical Engineering. He is a fellow of the American Institute for Medical and Biological Engineering.

Joseph J. Pancrazio

Joseph J. Pancrazio earned a B.S. degree in Electrical Engineering from the University of Illinois, Urbana, in 1984, and M.S. and Ph.D. degrees in Biomedical Engineering from the University of Virginia (UVa), Charlottesville, in 1988 and 1990, respectively. His Ph.D. training focused on the ion channel electrophysiology using the patch clamp technique. After postdoctoral training in pharmacology in the Department of Anesthesiology at UVa as a recipient of a National Research Service Award, he received a joint appointment in the Departments of Anesthesiology and Biomedical Engineering as an assistant professor of research at the University of Virginia in 1991, where he taught graduate level courses in Neuropharmacology and Bioelectronic Systems. In 1997, he joined Georgetown University Department of Biochemistry and Molecular Biology as an Assistant Professor working at the US Naval Research Laboratory (NRL) in Washington, DC. In 1998, he joined the NRL as a Principal Investigator at the Center for Bio/Molecular Science and Engineering, becoming the Head of Code 6920, the Laboratory of Biomolecular Dynamics, in 2002. At the NRL, Dr. Pancrazio led an extramurally supported project including biologists and engineers for the development and demonstration of a biosensor system based cultured neuronal networks for environmental threat

detection. He has authored over 70 peer-reviewed publications, several book chapters and review papers, and has two patents. Dr. Pancrazio joined the Repair and Plasticity Cluster of NINDS in January of 2004, where his primary research interests include: 1) neural engineering and neuroprosthesis; 2) novel neural repair technologies and biomaterials, and 3) neural information processing and control.

Jacob Rosen, Ph.D.

Jacob Rosen, Ph.D., is a Research Associate Professor of Electrical Engineering, with adjunct appointments in the Departments of Surgery, and Mechanical Engineering. He is a co-director of the Biorobotics lab (BRL) in the Dept. of Electrical Engineering and a director of engineering research and development at the University of Washington Institute for Surgical and Interventional Simulation. Dr. Rosen received his B.Sc. degree in Mechanical Engineering, M.Sc. and Ph.D. degrees in Biomedical Engineering from Tel-Aviv University in 1987, 1993 and 1997 respectively.

Dr. Rosen leads and serves as PI & co-PI of multiple interdisciplinary research efforts including but not limited to "Raven" - a portable surgical robot for open and minimally invasive telesurgery, the "Red DRAGON" - a multi modal simulator for minimally invasive surgery, along with an objective skill assessment methodology for medical simulators based on Markov Models, and neural control of upper limb wearable robot (Exoskeleton). His research interests focus on medical robotics & simulation, biorobotics, human centered robotics, surgical robotics, wearable robotics, rehabilitation robotics, neural control, and human-machine interface.

Smita Savant-Bhonsale, Ph.D.

Smita Savant-Bhonsale works for a Baltimore based Biotech Company, Theradigm, Inc. She is the VP of Research and General Manager for Theradigm. For last five years her research is focused on developing stem cell based therapies for central nervous system injuries and diseases. She has been doing research in stem cell field for the last seven years. Smita has experience working with number of different non-embryonic stem cell types. She has published her findings in peer-reviewed journals and presented her work at scientific conferences. Smita earned her PhD in Developmental Biology at Marquette University and received her post-doctoral training in Cell Biology at The Johns Hopkins University School of medicine.

Nitish Thakor, Ph.D.

Nitish V. Thakor received B. Tech. degree in electrical engineering from Indian Institute of Technology, Bombay, in 1974 and the Ph.D. degree in electrical and computer engineering from the University of Wisconsin, Madison, in 1981. He served on the faculty of Electrical Engineering and Computer Science of the Northwestern University between 1981 and 1983, and since then he has been with the Johns Hopkins University, School of Medicine, where he is currently serving as a Professor of Biomedical Engineering. He conducts research on neurological instrumentation, biomedical signal processing, micro and nanotechnologies, neural prosthesis, and clinical applications of neural and rehabilitation technologies. He has authored more than 170 peer-reviewed publications on these subjects. He is the Editor in Chief of IEEE Transactions on Neural and Rehabilitation Engineering. Currently he directs the Laboratory for Neuroengineering and is also the Director of the NIH Training Grant on

Neuroengineering. One of his current research projects, in collaboration with a multi-University consortium, funded by DARPA, is to develop a next generation neurally controlled upper limb prosthesis. He is actively engaged developing international scientific programs, collaborative exchanges, tutorials and conferences in the field of Biomedical Engineering. Dr. Thakor is a recipient of a Research Career Development Award from the National Institutes of Health and a Presidential Young Investigator Award from the National Science Foundation. He is a Fellow of the American Institute of Medical and Biological Engineering, IEEE and Founding Fellow of the Biomedical Engineering Society. He is also a recipient of the Centennial Medal from the University of Wisconsin School of Engineering, Honorary Membership from Alpha Eta Mu Beta Biomedical Engineering student Honor Society and Distinguished Service Award from IIT Bombay.

Commander Jack Tsao, M.D., Ph.D.

CDR Jack Tsao received his undergraduate and medical degrees from Harvard and doctorate from the University of Oxford, England. He completed neurology residency at the University of California-San Francisco and was then stationed at Naval Hospital Jacksonville, where he was neurology department head. While there, CDR Tsao completed a behavioral neurology fellowship at the University of Florida. He is currently Associate Professor of Neurology at the Uniformed Services University of the Health Sciences and is actively involved in medical student and resident education, clinical and basic science research, and telemedicine development. His clinical research is focused on treatments for phantom limb pain in amputees and methods for detecting and preventing traumatic brain injury.

AIMBE: The Advocate for Technology That Saves Lives

The American Institute for Medical and Biological Engineering was founded in 1991 to establish a clear and comprehensive identity for the field of medical and biological engineering — which is the bridge between the principles of engineering science and practice, and the problems and issues of biological and medical science and practice. Practical engagement of medical and biological engineers ranges from the fields of clinical medicine to food, agriculture and environmental bioremediation. AIMBE seeks to serve and coordinate a broad constituency of medical and biological scientists and practitioners, scientific and engineering societies, academic departments and industries.

As a national 501(c)3 organization based in Washington, DC, AIMBE's mission is to:

- Promote awareness of the field and its contributions to society in terms of new technologies that improve medical care and produce more and higher-quality food for people throughout the world;
- Work with lawmakers, government agencies and other professional groups to promote public polices that further advancements in the field;
- Strive to improve intersociety relations and cooperation within the field;
- Promote the national interest in science, engineering and education; and
- Recognize individual and group achievements and contributions to medical and biological engineering.

AIMBE is comprised of four sections:

- *The College of Fellows* — 1,000 individuals who are the outstanding biological and medical engineers in academia, industry and government. These leaders in the field have distinguished themselves through their contributions in research, industrial practice and/or education. Most Fellows come from the United States, but there are international Fellows.

The Chair of the College leads the committee that plans the overall program at AIMBE's Annual Event, held each winter in Washington.

- *The Academic Council* — Universities with educational programs in biological and medical engineering at the graduate or undergraduate level, over 100 member institutions in total. Representatives to the Council generally are chairs of their departments and many are members of the College of Fellows. The Council considers issues ranging from curricular standards and accreditation to employment of graduates and funding for graduate study. The Academic Council meets at the Annual Event and at another scientific meeting during the year.
- *The Council of Societies* — AIMBE's mechanism for coordinating interaction among 19 scientific organizations in medical and biological engineering. The purposes of the Council are to provide a collaborative forum for the establishment of society member positions on issues affecting the field of medical and biological engineering, to foster intersociety dialogue and cooperation that provides a cohesive public representation for medical and biological engineering, and to provide a way to coordinate activities of member societies with the activities of academia, government, the health care sector, industry and the public and private biomedical communities. The Council of Societies meets at AIMBE's Annual Event.
- *The Industry Council* — A forum for dialogue between industry, academia and government in order to identify and act on common interests that will advance the field of medical and biological engineering and contribute to public health and welfare. Industrial organizations may be members of the Industry Council if they have substantial and continuing professional interest in the field of medical and biological engineering. The Industry Council meets at the Annual Event.

The AIMBE Board of Directors oversees the work of the College of Fellows and the three Councils. The Board consists of a President who is assisted by two Past Presidents, the President-Elect, four Vice-Presidents at Large, a Secretary-Treasurer and the Chair of the College of Fellows — all of whom are elected by the Fellows. The Board also includes the chairs of the other Councils and chairs of all standing committees. AIMBE's day-to-day operations are supervised by the Executive Director.

For additional information about AIMBE's mission, membership and accomplishments, visit www.aimbe.org on the Web.

US MRMC TATRC

The Telemedicine and Advanced Technology Research Center (TATRC), a subordinate element of the United States Army Medical Research and Materiel Command (USAMRMC), is charged with managing core Research Development Test and Evaluation (RDT&E) and congressionally mandated projects in telemedicine and advanced medical technologies. To Support its research and development efforts, TATRC maintains a productive mix of partnerships with federal, academic, and commercial organizations. TATRC also provides short duration, technical support (as directed) to federal and defense agencies; develops, evaluates, and demonstrates new technologies and concepts; and conducts market surveillance with a focus on leveraging emerging technologies in healthcare and healthcare support. Ultimately, TATRC's activities strive to make medical care and services more accessible to soldiers, sailors, marines, and airmen; reduce costs, and enhance the overall quality of military healthcare.

Appendix E
List of Attendees

AIMBE-Military Collaboration Registration			
First Nam	*Last Name*	*Suffix*	*Title*
Jeffrey M.	Anderson		Associate Director, NanoScience Technology Center
James	Anderson	M.D., Ph.D.	Professor
James F.	Antaki		Professor
Konstantinos	Arfanakis	Ph.D.	Assistant Professor
Brenda	Bart-Knauer	M.D.	Senior Clinical Consultant
Paul	Basser	Ph.D.	Principle Investigator
Theodore	Berger		Director
Yudhijit	Bhattacharjee		
Terry	Bice		Technical Manager
Martha	Bidez	Ph.D.	President
Elena	Bodnar	M.D.	
Sylvain	Cardin		Senior Medical Science and Tech Consultant
Ibolja	Cernak		Program Manager
Laurence	Clarke	Ph.D.	
Gary	Cleary		Chief Technical Officer
Mark	Cohen	Ph.D.	
Kenneth C.	Curley	M.D.	
Donna	Dean	Ph.D.	Senior Science Advisor
Avraham	Dilmanian	Ph.D.	Scientist
Richard	Dutton	M.D, MBA	
R. Daniel	Ferguson		
Scott	Frey	Ph.D.	
William A.	Friedman	Ph.D.	
Kyle	Fritt		Research Engineer
Alisa	Gean	M.D.	
John	Granacki		Division Director
Bradley	Greger	Ph.D.	Assistant Professor
Nita	Grimsley		Project Manager
Terrie	Grissom		Program Operations Manager
Warren	Grundfest	M.D., F.A.C.S.	
Anthony	Guiseppi-Elie	Sc.D.	Professor
Ronald L.	Hayes	Ph.D.	
James	Hickman	Ph.D.	Professor
Andreas H.	Hielscher	Ph.D.	

David	Hovda	Ph.D.	
Kurtulus	Izzetoglu		Research Engineer
E. Duco	Jansen		Professor
Kelly	Kennedy		Reporter
Ron	Kikinis	M.D.	
Makoto	Kikuchi	Ph.D.	Professor, Department of Medical Engineering
Vassilis	Koliatsos	M.D.	
Michelle	Laplaca		Associate Director
Raphael	Lee	M.D., Sc.D.	Professor of Surgery and Biomechanics
Martha	Lenhart	M.D., Ph.D.	
Geoffrey	Ling	M.D., Ph.D.	
Mary	Lopez		
Kenneth	Lutchen		Dean
Igor	Lyashenko		
Mark B.	Lyles	Ph.D.	
Anil	Maybhate		Scientist
Mike	McLoughlin		Biomedicine Branch Head
David	Meaney	Ph.D.	Chairman
Andrew	Merkle		Biomechanical Engineer
Anna	Merzagora		Research Assistant
David	Mogul	Ph.D.	Associate Professor
David	Moore	M.D., Ph.D.	
Pierre	Mourad	Ph.D.	
Seong K.	Mun	Ph.D.	
Matthew R.	Myers		Research Physicist
Joel	Myklebust	Ph.D.	
Troy	Nagle		Professor
Margaret	Natarajan	M.D.	
Gail K.	Naughton		
Richard	Normann	Ph.D.	Professor
Amy	Nyswaner	RN	RN
Paul	Pasquina	Ph.D.	
P. Hunter	Peckham	Ph.D.	Director
Kambiz	Pourrezaei		Professor
J. Gregory	Rose		Biomedical Engineer
Jacob	Rosen	Ph.D.	
M. Steve	Rountree		Program Manager

Subrata	Saha		
Smita	Savant-Bhonsale	Ph.D.	
John	Schenck	M.D., Ph.D.	Senior Scientist
Susan	Schwartz-Giblin	Ph.D.	Dean
Lawrence	Shepp	Ph.D.	Professor
Nancy	Shinowara	Ph.D.	Program Director
Wendy	Shore		
Dexter	Smith		Biomedicine Business Area Executive
Davood	Tashayyod		Entrepreneur in Residence
Nitish	Thakor	Ph.D.	Professor
Frank	Tortella	Ph.D.	Chief
Jack	Tsao	M.D., Ph.D.	
Bob	Vandre		
Santosh	Venkatesha		
Liming	Voo		Biomechanical Engineer
Kirby	Vosburgh	Ph.D.	Associate Director
Tim	Walilko		
Jennifer	Wayne	Ph.D.	Professor
Robert	Wellek	Ph.D.	Deputy Director
Bruce	Wheeler	Ph.D.	Professor

Affiliation	***Address1***	***Address2***
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Case Western Reserve University	Dept. of Pathology	2103 Cornell Rd.
Carnegie Mellon University	5000 Forbes Avenue	
Illinois Institute of Technology	10 West 32nd Street	E1-116
TATRC/The Geneva Foundation	P.O. Box 8512	
NIH/NICHD	13 South Drive	Bldg. 13 Rm 3W16
University Of Southern California	1042 Downey Way	
Science Magazine	1200 New York Ave., NW	
John Hopkins University	11100 John Hopkins Road	MP2-N143
Bidez & Associates	2100 3rd Avenue N.	Suite 410
University of Chicago	5841 South Maryland Avenue	MC 6035
TATRC		
John Hopkins University	11100 John Hopkins Road	MP2-N143
NIH National Cancer Institute		
Corium International, Inc.	2686 Middlefield Rd.	Suite G
University of California, San Fransico		
TATRC		
Lewis-Burke Associate	1341 G Street NW	Eighth Floor
Brookhaven National Laboratory	Bldg. 490,	30 Bell Avenue
University of Maryland Medical System		
Physical Sciences Inc.		
University of Oregon		
McKnight Brain Institute		
Infinite Biomedical Technologies	3600 Clipper Mill Rd., Ste. 410	
University of California, San Fransico		
USC/ISI	4676 Admiralty Way, Ste. 1001	
University of Utah	20 South 2030 East	
Telemedicine & Advanced Technology Research Center	Bldg. 1054, Patchel Street	
John Hopkins University	11100 John Hopkins Road	MP2-N143
University of California, Los Angeles		
Clemson University	Clemson C3B	132 Earle Hall
Banyan Bio, Inc.		
University of Central Florida	12424 Research Parkway	Suite 400
Columbia University		

UCLA Brain Injury Research Center		
Drexel University	3141 Chestnut Street	
Vanderbilt University	VU Station B#351631	
Military Times		
Brigham Women's Hospital		
National Defense Medical College	3-2 Namiki	
John Hopkins University	720 Rutland Avenue	
Georgia Institute of Technology	313 Ferst Drive	
University of Chicago	MC6035	5841 S. Maryland Avenue, Suite J641
Borden Institute	6900 Georgia Avenue NW	Bldg. 11, Room 1-111
Defense Agency Research Projects Agenda		
Army Occupational Therapy Consultant		
Boston University College of Engineering	44 Cummington Street	ERB 601
Russian Embassy	2650 Wisconsin Ave., NW	
US Navy	2300 E Street NW	
Infinite Biomedical Technologies	3600 Clipper Mill Rd.	
John Hopkins University	11100 John Hopkins Road	MP2-N143
University of Pennsylvania	210 S. 33rd Street	Room 240, Skirkanich Hall
John Hopkins University	11100 John Hopkins Road	MP2-N143
Drexel University	3141 Chestnut Street	
Illinois Institute of Technology	10 West 32nd Street	Room 116
Defense and Veterans Brain Injury Center		
University of Washington		
Georgetown University		
U.S. FDA/CDRH	10903 New Hampshire Avenue	
US Federal Drug Administration		
UNC-NCSU	18 Heath Place	
Infinite Biomedical Technologies	3600 Clipper Mill Rd.	
San Diego State University	5500 Campanile Drive	
University of Utah	20 South 2030 East	
TATRC	1054 Patchel Street	
Walter Reed Army Medical Center		
Case Western Reserve University	Metro Health Medical Center	2500 Metro Health Drive
Drexel University	3141 Chestnut Street	
John Hopkins	600 N. Wolfe Street	Phipps 174
University of Washington		
John Hopkins University	11100 John Hopkins Road	MP2-N143

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Theradigm		
General Electric Global Research	1 Research Circle	
SUNY Downstate Medical Center	450 Clarkson Ave.	
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NIH/NICHD	6100 Executive Blvd.	2A03
John Hopkins University	600 N. Wolfe Street	Phipps 174
John Hopkins University	11100 John Hopkins Road	MP2-N143
Drexel University	3141 Chestnut Street	
John Hopkins University	720 Rutland Avenue	
Walter Reed Army Institute of Research	503 Robert Grant Ave.	
Uniformed Services University of the Health Sciences		
US Armedical Research & Material Command	504 Scott Street	
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CIMIT	165 Cambridge Street	Suite #702
Applied Research Association	1848 Lockhill Selma	Suite 102
Virginia Commonwealth University	Box 843067	
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			301-619-6968	cardin@tatrc.org		
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			301-696-9240	curley@tatrc.org		
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			571-201-6408	mlopez@usuhs.mil		
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Appendix F
Coverage in Military Times

Testing breakthrough for mild TBI

By Kelly Kennedy - Staff writer
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After months of military officials and medical personnel lamenting the lack of an immediate, unequivocal, physical proof of mild traumatic brain injury, an anesthesiologist thinks he has found a solution.

And it may be as simple as two sensors and a BlackBerry.

Dr. Richard Dutton heads up trauma anesthesiology at the R. Adams Cowley Shock Trauma Center at the University of Maryland and sees about 4,000 people a year who doctors believe have a brain injury. But without a CT scan or an MRI, it's hard to immediately tell for sure — especially if, as is the case in most trauma situations, doctors are also worried about broken bones, ruptured organs or heavy bleeding. And about 3,000 of those cases are mild TBI, which doesn't show up on a scan.

So Dutton and a team of engineers decided to see if they could use sonar to "listen" for differences in healthy brains and injured brains. They used a headband with sensors to pick up the sound transmitted through the brain with sonar and then analyzed the data fed back into a computer. The Air Force paid for the research.

"We'd 'ping' them with sonar and then listen," Dutton said Feb. 20 at an American Institute for Medical and Biological Engineering conference.

They hoped to detect differences in brain mass, but they didn't come up with much. Then, one day, they'd stopped the "pings" but left the sensors on, so the computer was just "listening" to the normal flow of the brain. Somebody looked at the computer and noticed a regular pattern of bandwidths. "We said, 'Hey, that's important,'" Dutton said.

The sensors apparently were picking up tiny movements caused by blood coursing through the vessels in the brain. Dutton said this guess — that it is blood causing the movement — is based on previous studies as well as mathematical modeling. "It's like a digital stethoscope," he said.

They decided to "listen" to more patients with the "Brain Acoustic Monitor." Armed with the knowledge that normal brains have even, regulated wavelengths, the researchers listened to the brains of 30 patients, all with severe TBI. The 15 who had normal signals five days after injury got better, while the 15 who were still abnormal did not improve clinically.

"All those patients died or left for rehabilitation in persistently vegetative states," Dutton said. Those patients, he believes, had turbulent blood flow in the brain, as opposed to the smooth blood flow of a normal brain. Brain injuries typically involve bruising, which causes blood vessels to burst.

The bigger problem, especially for the military, has always been mild TBI. Doctors typically can't see mild TBI, even with a scan. But they know it's important not to send a service member back out on patrol with a mild TBI because injuries caused by mild TBI are cumulative; even a slight second head injury can cause death for someone with an already damaged brain, and no one wants to go on patrol with someone whose vision is blurry or who has short-term memory loss.

When Dutton and the engineers tried out their equipment on people they believed to have mild TBIs, they found turbulent blood flow — or irregular bandwidths — on the Brain Acoustic Monitor.

"You hit your head, your BAM becomes abnormal," Dutton said. "We think we may have an objective marker for brain injury. This is pretty exciting stuff."

And it's completely portable, which could be good news for troops in Iraq and Afghanistan. In Iraq, there's one CT scan — in Balad — and no MRI machine. Medics don't have access to the heavy, expensive equipment.

But information gained from BAM comes from two sensors placed on the forehead, which is then processed with a laptop or a BlackBerry. They're working on making it even more medic-friendly by creating a simple "red means no-go, green means go" system to determine whether a person needs to go see a doctor or is good to go back on patrol.

BAM has been tested on more than 400 patients. It's going through the Food and Drug Administration approval process now, but Dutton said there are some issues. It doesn't predict the severity of an injury, only that there is one. He said his team hopes to test the use of more sensors placed over more areas of the skull to see if they can detect regional damage. So far, they've only tried that on bald patients because hair gets in the way of the signal.

But just determining that there is an injury is huge, especially for mild TBIs. "Mild" is a misnomer because it can mean anything from a soldier who bangs his head but has nothing more than a passing headache to a Marine who bangs his head and has headaches, permanent short-term memory loss and mild seizures.

Some symptoms of mild TBI also are similar to those of post-traumatic stress disorder, so people can be misdiagnosed.

Thousands of troops who have served in Iraq and Afghanistan are believed to have suffered mild TBI from accidents or explosions.

Dutton's presentation was not the only one to cause excitement at the conference. Marilyn Kraus, associate professor of psychiatry and neurology at the University of Illinois at Chicago, talked about how differences in white brain matter correspond with cognitive and behavioral issues, and therefore looking closely at white matter could help differentiate between PTSD and mild TBI symptoms.

She used Diffusion Sensor Imaging to look at the density of white brain matter and found that scans of people with mild TBI were "significantly different" from normal scans. The differences could also point to future problems, such as epilepsy or dementia.

And David Hovda, professor of surgery at the University of California, said a closer look at brain activity showed that those with brain injuries burn lactate for energy as their metabolic rate declines, which suggests that metabolic therapy through an IV might be important for treating brain injuries. A normal brain uses glucose for energy.

"Fuel is dictated by the needs of the tissue, not by what we think it needs," Hovda said. "TBI victims tend to come in hyperglycemic, so doctors tend to keep insulin levels low. We may need to look at it differently."